10/020450

```
FILE 'HOME' ENTERED AT 18:50:11 ON 15 JUN 2003

=> file medicine
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'ADISCTI' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 Adis Data Information BV

FILE 'ADISINSIGHT' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 Adis Data Information BV

FILE 'ADISNEWS' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 Adis Data Information BV

FILE 'BIOSIS' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 BIOLOGICAL ABSTRACTS INC. (R)

FILE 'BIOTECHNO' COULD NOT BE ENTERED

FILE 'CANCERLIT' ENTERED AT 18:50:25 ON 15 JUN 2003

FILE 'CAPLUS' ENTERED AT 18:50:25 ON 15 JUN 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'CEN' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 American Chemical Society (ACS)

FILE 'DDFB' ACCESS NOT AUTHORIZED

FILE 'DDFU' COULD NOT BE ENTERED

FILE 'DGENE' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 DERWENT INFORMATION LTD

FILE 'DRUGB' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 THOMSON DERWENT

FILE 'DRUGLAUNCH' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 IMSWORLD Publications Ltd

FILE 'DRUGMONOG2' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 IMSWORLD Publications Ltd

FILE 'DRUGNL' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 IMSWORLD Publications Ltd

FILE 'DRUGU' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 THOMSON DERWENT

FILE 'EMBAL' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 Elsevier Science B.V.  All rights reserved.

FILE 'EMBASE' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 Elsevier Science B.V.  All rights reserved.

FILE 'ESBIOBASE' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 Elsevier Science B.V., Amsterdam. All rights reserved.

FILE 'IFIPAT' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 IFI CLAIMS(R) Patent Services (IFI)
```

FILE 'IPA' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 American Society of Hospital Pharmacists (ASHP)

FILE 'JICST-EPLUS' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 Japan Science and Technology Corporation (JST)

FILE 'KOSMET' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 International Federation of the Societies of Cosmetics Chemists

FILE 'LIFESCI' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 Cambridge Scientific Abstracts (CSA)

FILE 'MEDICONF' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (c) 2003 FAIRBASE Datenbank GmbH, Hannover, Germany

FILE 'MEDLINE' ENTERED AT 18:50:25 ON 15 JUN 2003

FILE 'NAPRALERT' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 Board of Trustees of the University of Illinois,
University of Illinois at Chicago.

FILE 'NLDB' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 Gale Group. All rights reserved.

FILE 'NUTRACEUT' ENTERED AT 18:50:25 ON 15 JUN 2003
Copyright 2003 (c) MARKETLETTER Publications Ltd. All rights reserved.

FILE 'PASCAL' ENTERED AT 18:50:25 ON 15 JUN 2003
Any reproduction or dissemination in part or in full,
by means of any process and on any support whatsoever
is prohibited without the prior written agreement of INIST-CNRS.
COPYRIGHT (C) 2003 INIST-CNRS. All rights reserved.

FILE 'PCTGEN' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 WIPO

FILE 'PHARMAML' ENTERED AT 18:50:25 ON 15 JUN 2003
Copyright 2003 (c) MARKETLETTER Publications Ltd. All rights reserved.

FILE 'PHIC' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 PJB Publications Ltd. (PJB)

FILE 'PHIN' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 PJB Publications Ltd. (PJB)

FILE 'SCISEARCH' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT 2003 THOMSON ISI

FILE 'TOXCENTER' ENTERED AT 18:50:25 ON 15 JUN 2003
COPYRIGHT (C) 2003 ACS

FILE 'USPATFULL' ENTERED AT 18:50:25 ON 15 JUN 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 18:50:25 ON 15 JUN 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

=> s cerebral ischemia
L1 81392 CEREBRAL ISCHEMIA

=> s cerebra ischaemia
L2 0 CEREBRA ISCHAEMIA

=> s cerebral ischaemia
L3 28724 CEREBRAL ISCHAEMIA

```
=> s beta tocopherol
L4        2477 BETA TOCOPHEROL

=> s delta tocopherol
L5        3402 DELTA TOCOPHEROL

=> s gamma tocopherol
L6        7759 GAMMA TOCOPHEROL

=> s neuronal damage
L7       31222 NEURONAL DAMAGE

=> s neuronal death
L8       35801 NEURONAL DEATH

=> s l1 or l2
L9       81392 L1 OR L2

=> s l1 and l6 and l7
L10          7 L1 AND L6 AND L7

=> d l10 1-7 bib abs kwic

L10  ANSWER 1 OF 7  IFIPAT  COPYRIGHT 2003 IFI
AN    10199343  IFIPAT;IFIUDB;IFICDB
TI    COMPOSITIONS AND METHODS FOR THE PREVENTION AND TREATMENT OF
      CEREBRAL ISCHEMIA
INF   Boddupalli; Sekhar, San Jose, CA, US
      Brown; Lesley A., San Jose, CA, US
      Del Balzo; Ughetta, Morgan Hill, CA, US
      Flaim; Stephen, San Diego, CA, US
      Miller; Guy Michael, San Jose, CA, US
      Wang; Bing, Cupertino, CA, US
IN    Boddupalli Sekhar; Brown Lesley A; Del Balzo Ughetta; Flaim Stephen;
      Miller Guy Michael; Wang Bing
PAF   Unassigned
PA    Unassigned Or Assigned To Individual (68000)
AG    Gladys H. Monroy Morrison & Foerster LLP, 755 Page Mill Road, Palo Alto,
      CA, 94304-1018 US
PI    US 2002143049   A1  20021003
AI    US 2001-20450       20011214
PRAI  US 2000-256269P     20001215 (Provisional)
      US 2001-296580P     20010606 (Provisional)
FI    US 2002143049       20021003
DT    Utility; Patent Application - First Publication
FS    CHEMICAL
      APPLICATION
CLMN  57
GI     4 Figure(s).
     FIG. 1 shows the effect of gamma-tocopherol and its
      metabolite, gamma-carboxy ethyl hydroxy chroman (gamma-CEHC), on the
      volumetric comparison of total infarct with administration of
      gamma-tocopherol and gamma-CEHC at the time of Middle
      Cerebral Artery Occlusion (MCAO) as described in Example 2.
     FIG. 2 shows the effect of gamma-tocopherol and its
      metabolite, gamma-CEHC, on the volumetric comparison of total infarct
      with administration of gamma-tocopherol and
      gamma-CEHC at reperfusion as described in Example 2.
     FIG. 3 illustrates 5 general formulas of tocopherol metabolites.
     FIG. 4 shows the effect of gamma-tocopherol on stroke
      protection as measured in cerebral ischemia MCAO
      model.
AB    The present invention provides compositions and methods for the treatment
      of cerebral ischemia. In particular, the present
      invention provides gamma-, beta-, or delta-tocopherol enriched tocopherol
      compositions and gamma-, beta-, or delta-tocopherol metabolite enriched
      compositions and methods for their use in preventing or treating a
```

cerebral ischemic condition. The present invention also provides pharmaceutical compositions comprising gamma-, beta-, or delta-tocopherol enriched tocopherol composition or a gamma-, beta-, or delta-tocopherol metabolite enriched composition in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition.

CLMN 57 4 Figure(s).

FIG. 1 shows the effect of **gamma-tocopherol** and its metabolite, gamma-carboxy ethyl hydroxy chroman (gamma-CEHC), on the volumetric comparison of total infarct with administration of **gamma-tocopherol** and gamma-CEHC at the time of Middle Cerebral Artery Occlusion (MCAO) as described in Example 2.

FIG. 2 shows the effect of **gamma-tocopherol** and its metabolite, gamma-CEHC, on the volumetric comparison of total infarct with administration of **gamma-tocopherol** and gamma-CEHC at reperfusion as described in Example 2.

FIG. 3 illustrates 5 general formulas of tocopherol metabolites.

FIG. 4 shows the effect of **gamma-tocopherol** on stroke protection as measured in **cerebral ischemia** MCAO model.

TI COMPOSITIONS AND METHODS FOR THE PREVENTION AND TREATMENT OF **CEREBRAL ISCHEMIA**

AB The present invention provides compositions and methods for the treatment of **cerebral ischemia**. In particular, the present invention provides gamma-, beta-, or delta-tocopherol enriched tocopherol compositions and gamma-, beta-, or delta-tocopherol metabolite enriched. . . . or delta-tocopherol enriched tocopherol composition or a gamma-, beta-, or delta-tocopherol metabolite enriched composition in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition.

GI 4 Figure(s).

FIG. 1 shows the effect of **gamma-tocopherol** and its metabolite, gamma-carboxy ethyl hydroxy chroman (gamma-CEHC), on the volumetric comparison of total infarct with administration of **gamma-tocopherol** and gamma-CEHC at the time of Middle Cerebral Artery Occlusion (MCAO) as described in Example 2.

FIG. 2 shows the effect of **gamma-tocopherol** and its metabolite, gamma-CEHC, on the volumetric comparison of total infarct with administration of **gamma-tocopherol** and gamma-CEHC at reperfusion as described in Example 2.

FIG. 3 illustrates 5 general formulas of tocopherol metabolites.

FIG. 4 shows the effect of **gamma-tocopherol** on stroke protection as measured in **cerebral ischemia** MCAO model.

ECLM . . . comprising administering to the subject an effective amount of a non-alpha tocopherol enriched tocopherol composition, and by said administering, reducing **neuronal damage** related to said cerebral ischemic condition.

ACLM 2. The method of claim 1 wherein the non-alpha tocopherol enriched tocopherol composition is a **gamma-tocopherol** enriched tocopherol composition.

3. The method of claim 1 wherein the non-alpha tocopherol enriched tocopherol composition is a **gamma-tocopherol** metabolite enriched composition.

8. The method of claim 3 wherein said **gamma-tocopherol** metabolite is gamma-CEHC.

11. The method of claim 1 wherein the **cerebral ischemia** is due to a spasm of the coronary vasculature.

15. The method of claim 2 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 60% **gamma-tocopherol**.

16. The method of claim 2 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 65% **gamma-tocopherol**.

17. The method of claim 2 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 70% **gamma-tocopherol**.

18. The method of claim 2 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 75% **gamma-tocopherol**.
19. The method of claim 2 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 80% **gamma-tocopherol**.
20. The method of claim 2 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 85% **gamma-tocopherol**.
21. The method of claim 2 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 90% **gamma-tocopherol**.
22. The method of claim 2 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 95% **gamma-tocopherol**.
23. The method of claim 2 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 98% **gamma-tocopherol**.
24. The method of claim 3 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 60% **gamma-tocopherol** metabolite.
25. The method of claim 3 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 65% **gamma-tocopherol** metabolite.
26. The method of claim 3 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 70% **gamma-tocopherol** metabolite.
27. The method of claim 3 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 75% **gamma-tocopherol** metabolite.
28. The method of claim 3 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 80% **gamma-tocopherol** metabolite.
29. The method of claim 3 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 85% **gamma-tocopherol** metabolite.
30. The method of claim 3 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 90% **gamma-tocopherol** metabolite.
31. The method of claim 3 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 95% **gamma-tocopherol** metabolite.
32. The method of claim 3 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 98% **gamma-tocopherol** metabolite.

L10 ANSWER 2 OF 7 USPATFULL
AN 2002:273412 USPATFULL
TI Therapeutic methods employing disulfide derivatives of dithiocarbamates and compositions useful therefor
IN Lai, Ching-San, Encinitas, CA, UNITED STATES
Vassilev, Vassil, San Diego, CA, UNITED STATES
PA Medinox, Inc. (U.S. corporation)
PI US 2002151540 A1 20021017
AI US 2002-44096 A1 20020111 (10)
RLI Division of Ser. No. US 2000-565665, filed on 5 May 2000, ABANDONED
DT Utility
FS APPLICATION
LREP Stephen E. Reiter, Foley & Lardner, P.O. Box 80278, San Diego, CA, 92138-0278
CLMN Number of Claims: 17
ECL Exemplary Claim: 1
DRWN 5 Drawing Page(s)
LN.CNT 2548
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides a novel dithiocarbamamte disulfide dimer useful in various therapeutic treatments, either alone or in combination

with other active agents. In one method, the disulfide derivative of a dithiocarbamate is coadministered with an agent that inactivates (or inhibits the production of) species that induce the expression of nitric oxide synthase to reduce the production of such species, while, at the same time reducing nitric oxide levels in the subject. In another embodiment, free iron ion levels are reduced in a subject by administration of a disulfide derivative of a dithiocarbamate(s) to scavenge free iron ions, for example, in subjects undergoing anthracycline chemotherapy. In another embodiment, cyanide levels are reduced in a subject by administration of a disulfide derivative of a dithiocarbamate so as to bind cyanide in the subject. In a further aspect, the present invention relates to compositions and formulations useful in such therapeutic methods.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . of inflammatory cytokines, toxic shock syndrome, adult respiratory distress syndrome, cachexia, myocarditis, autoimmune disorders, eczema, psoriasis, heart failure, dermatitis, urticaria, **cerebral ischemia**, systemic lupus erythematosis, AIDS, AIDS dementia, neurodegenerative disorders (e.g., chronic neurodegenerative disease), chronic pain, priapism, cystic fibrosis, amyotrophic lateral sclerosis,. . .

DETD . . . range of disease states and/or indications, such as, for example, septic shock, hemorrhagic shock, anaphylactic shock, toxic shock syndrome, ischemia, **cerebral ischemia**, administration of cytokines, overexpression of cytokines, ulcers, inflammatory bowel disease (e.g., gastritis, ulcerative colitis or Crohn's disease), diabetes, arthritis, asthma,. . .

DETD . . . Fujimycin, Prograf, IL-2 fusion toxin, DAB.sub.389IL-2, and the like), IL-4 antagonists (e.g., IL-4 fusion toxin, DAB.sub.389IL-4, and the like), immune-mediated **neuronal damage** inhibitors, immunoglobins, immunostimulants (e.g., poly-ICLC, edelfosine, ET-18-OCH3, ET-18-OME, and the like), immunosuppressants (e.g., azathioprine, castanospermine, tacrolimus, FK-506, Fujimycin, Prograf, anti-leukointegrin. . .

DETD . . . myocarditis, multiple sclerosis, diabetes mellitus, autoimmune disorders, eczema, psoriasis, glomerulonephritis, heart failure, heart disease, atherosclerosis, Crohn's disease, dermatitis, urticaria, ischemia, **cerebral ischemia**, systemic lupus erythematosis, AIDS, AIDS dementia, chronic neurodegenerative disease, chronic pain, priapism, cystic fibrosis, amyotrophic lateral sclerosis, schizophrenia, depression, premenstrual. . .

DETD [0196] Antioxidants contemplated for use in the above-described topical formulations include superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, **.gamma.-tocopherol**, .alpha.-tocopherol, ubiquinol 10, ubiquinone 10, ascorbic acid, uric acid, glutathione, and the like.

L10 ANSWER 3 OF 7 USPATFULL

AN 2002:259473 USPATFULL

TI Compositions and methods for the prevention and treatment of **cerebral ischemia**

IN Miller, Guy Michael, San Jose, CA, UNITED STATES
Brown, Lesley A., San Jose, CA, UNITED STATES
Del Balzo, Ughetta, Morgan Hill, CA, UNITED STATES
Flaim, Stephen, San Diego, CA, UNITED STATES
Boddupalli, Sekhar, San Jose, CA, UNITED STATES
Wang, Bing, Cupertino, CA, UNITED STATES

PI US 2002143049 A1 20021003

AI US 2001-20450 A1 20011214 (10)

PRAI US 2000-256269P 20001215 (60)
US 2001-296580P 20010606 (60)

DT Utility

FS APPLICATION

LREP Gladys H. Monroy, Morrison & Foerster LLP, 755 Page Mill Road, Palo Alto, CA, 94304-1018

CLMN Number of Claims: 57

ECL Exemplary Claim: 1
DRWN 4 Drawing Page(s)
LN.CNT 2288
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides compositions and methods for the treatment of **cerebral ischemia**. In particular, the present invention provides gamma-, beta-, or delta-tocopherol enriched tocopherol compositions and gamma-, beta-, or delta-tocopherol metabolite enriched compositions and methods for their use in preventing or treating a cerebral ischemic condition. The present invention also provides pharmaceutical compositions comprising gamma-, beta-, or delta-tocopherol enriched tocopherol composition or a gamma-, beta-, or delta-tocopherol metabolite enriched composition in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Compositions and methods for the prevention and treatment of **cerebral ischemia**
AB The present invention provides compositions and methods for the treatment of **cerebral ischemia**. In particular, the present invention provides gamma-, beta-, or delta-tocopherol enriched tocopherol compositions and gamma-, beta-, or delta-tocopherol metabolite enriched. . . or delta-tocopherol enriched tocopherol composition or a gamma-, beta-, or delta-tocopherol metabolite enriched composition in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition.
SUMM [0002] This invention generally relates to compositions and methods comprising **gamma-tocopherol** and/or a metabolite and/or a derivative thereof; beta-tocopherol and/or a metabolite and/or a derivative thereof; and delta-tocopherol and/or a metabolite and/or derivative thereof, for preventing or treating **cerebral ischemia** in a mammalian subject. The invention also relates to methods of making such compositions.
SUMM [0003] Ischemia may be defined as the loss of blood flow to a tissue. **Cerebral ischemia**, also known as stroke, is the interruption or reduction of blood flow in the arteries feeding the brain. Loss of. . .
SUMM . . . 1501S-1509S. Alpha-tocopherol also functions as a scavenger of active nitrogen species (Halliwell et al. (1992) FEBS Lett. 313:62-66) and a **gamma-tocopherol** metabolite is an alleged natriuretic (Wechter et al. (1996) Proc. Natl. Acad. Sci. USA 93:6002-6007). See also U.S. Pat. No.. . . 6,150,402; 6,083,982; 6,048,891, and 6,242,479 specifically incorporated herein in their entirety. Alpha-tocopherol has been alleged to have an effect on **cerebral ischemia**. Yamamoto et al., 1983, Stroke, vol. 14:977-982; Hara et al., 1990, Brain Research, vol. 510:335-338; and Altura, et al., 1996,. . .
SUMM [0006] In the treatment of **cerebral ischemia**, free radical scavengers/antioxidants have been used to improve cerebral blood flow and/or neurological outcome. In general, the effects of these. . . (1991) Proc. Natl. Acad. Sci. USA 88:11158-11162. Other compounds, such as lubeluzole, have been shown to have clinical benefit for **cerebral ischemia** but with a very narrow margin of safety. Diener et al. (1995) Stroke 26:30.
SUMM [0007] **Cerebral ischemia** is one of the major causes of human neurological morbidity and mortality with poor prognosis associated with stroke recovery. Thus,. . . for identification of effective compositions and methods which aid in the survival and recovery of cells during injury associated with **cerebral ischemia** or for mammalian subjects at risk for injury associated with **cerebral ischemia**.
SUMM [0009] The present invention relates to compositions and methods for the treatment and prevention of **cerebral ischemia** in a mammalian subject. Accordingly, the present invention provides methods for treating and/or ameliorating the symptoms of a cerebral ischemic. . . comprising administering to the subject an effective amount of a

non-alpha tocopherol enriched tocopherol composition, and by said administering, reducing **neuronal damage** related to said cerebral ischemic condition. In some embodiments, the non-alpha tocopherol enriched tocopherol composition is a **gamma-tocopherol** enriched tocopherol composition. In other embodiments, the non-alpha tocopherol enriched tocopherol composition is a **gamma-tocopherol** metabolite enriched composition. In additional embodiments, the non-alpha tocopherol enriched tocopherol composition is a beta-tocopherol enriched tocopherol composition. In further. . .

SUMM . . . occlusion of the cerebral vasculature and in other embodiments, the occlusion is due to a thromboembolis. In further embodiments, the **cerebral ischemia** is due to a spasm of the coronary vasculature. In additional embodiments, the cerebral ischemic condition is secondary to a. . .

SUMM [0011] In some aspects of the present invention, a **gamma tocopherol** enriched tocopherol composition comprises at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% **gamma-tocopherol**. In other aspects, a beta-tocopherol enriched tocopherol composition comprises at least 50%, at least 55%, at least 60%, at least. . . least 80%, at least 85%, at least 90%, at least 95%, or at least 98% delta-tocopherol. In further aspects, a **gamma tocopherol** metabolite enriched composition comprises at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% **gamma-tocopherol** metabolite. In some embodiments, the **gamma-tocopherol** metabolite is gamma-CEHC. In other aspects, a beta-tocopherol metabolite enriched composition comprises at least 50%, at least 55%, at least. . .

SUMM [0014] In other aspects the present invention provides **gamma-tocopherol** enriched tocopherol compositions comprising **gamma tocopherol** in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition. In further embodiments, the present invention provides beta-tocopherol enriched tocopherol compositions comprising beta tocopherol in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition. In further embodiments, the present invention provides delta-tocopherol enriched tocopherol compositions comprising delta tocopherol in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition.

SUMM [0015] The other aspects the present invention provides **gamma-tocopherol** metabolite or derivative enriched compositions comprising a **gamma tocopherol** metabolite or derivative in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition. In preferred embodiments, the **gamma-tocopherol** metabolite is gamma-CEHC. In further embodiments, the present invention provides beta-tocopherol metabolite or derivative enriched compositions comprising a beta tocopherol metabolite or derivative in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition. In further embodiments, the present invention provides delta-tocopherol metabolite or derivative enriched compositions comprising a delta tocopherol metabolite or derivative in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition.

DRWD [0016] FIG. 1 shows the effect of **gamma-tocopherol** and its metabolite, gamma-carboxy ethyl hydroxy chroman (gamma-CEHC), on the volumetric comparison of total infarct with administration of **gamma-tocopherol** and gamma-CEHC at the time of Middle Cerebral Artery Occlusion (MCAO) as described in Example 2.

DRWD [0017] FIG. 2 shows the effect of **gamma-tocopherol** and its metabolite, gamma-CEHC, on the volumetric comparison of total infarct with administration of **gamma-tocopherol** and gamma-CEHC at reperfusion as described in Example 2.

DRWD [0019] FIG. 4 shows the effect of **gamma-tocopherol** on stroke protection as measured in **cerebral ischemia** MCAO model.

DETD . . . and non-naturally occurring mixtures of naturally-occurring compounds that can be used in nutritional and pharmaceutical compositions that are protective in **cerebral ischemia** (stroke). The present invention provides compositions and methods for preventing or treating **cerebral ischemia**, such as for example, by reducing neuronal cell death, reducing tissue edema, and/or reducing cognitive dysfunction associated with a cerebral. . .

DETD [0021] The present invention provides **gamma-tocopherol** enriched tocopherol compositions, beta-tocopherol enriched tocopherol compositions and delta-tocopherol enriched compositions and methods for using such compositions. In preferred embodiments, the **gamma-tocopherol** enriched tocopherol compositions of the present invention comprise at least 50% **gamma-tocopherol**, at least 55% **gamma-tocopherol**, at least 60% **gamma-tocopherol**, at least 65% **gamma-tocopherol**, at least 70% **gamma-tocopherol**, at least 75% **gamma-tocopherol**, at least 80% **gamma-tocopherol**, at least 85% **gamma tocopherol**, at least 90% **gamma-tocopherol**, at least 95% **gamma-tocopherol** and at least 98% **gamma-tocopherol**. **Gamma-tocopherol** enriched tocopherol compositions comprise less than 50% alpha-tocopherol, less than 45% alpha-tocopherol, less than 40% alpha-tocopherol, less than 35% alpha-tocopherol,. . . less than 20% alpha-tocopherol, less than 15% alpha-tocopherol, less than 10% alpha-tocopherol or less than 5% alpha-tocopherol. In some embodiments, **gamma-tocopherol** enriched tocopherol compositions comprise **gamma-tocopherol** as the sole active ingredient. As used herein, an "active ingredient" is one that is able to treat or prevent **cerebral ischemia** in a mammalian subject. In preferred embodiments, an active ingredient is able to reduce **neuronal damage** associated with **cerebral ischemia** at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%,. . .

DETD [0022] In additional preferred embodiments, a **gamma-tocopherol** enriched tocopherol composition comprises **gamma-tocopherol** in an amount effective to reduce neuronal cell death, reduce infarct size, reduce tissue edema associated with the cerebral ischemic condition, and/or reduce cognitive dysfunction and may further comprise a **gamma-tocopherol** metabolite and/or derivative and may further comprise alpha-tocopherol, beta-tocopherol and/or delta-tocopherol, and/or other ingredients. In other preferred embodiments, the **gamma-tocopherol** enriched tocopherol compositions of the present invention comprise additional active ingredients, and/or additional non-tocopherols. In some embodiments of **gamma-tocopherol** enriched tocopherol compositions, the **gamma-tocopherol** and additional ingredient(s) provide a synergistic effect. **Gamma-tocopherol** and an additional ingredient are considered to be synergistic when their combined effect is greater than additive of the individual. . .

DETD . . . at least 75% beta-tocopherol, at least 80% beta-tocopherol, at least 85% beta tocopherol, at least 90% beta-tocopherol, at least 95% **gamma-tocopherol** and at least 98% beta-tocopherol. Beta-tocopherol enriched tocopherol compositions comprise less than 50% alpha-tocopherol, less than 45% alpha-tocopherol, less than. . . ischemic condition, and/or reduce cognitive dysfunction and may further comprise a beta-tocopherol metabolite and/or derivative and may further comprise alpha-tocopherol, **gamma-tocopherol** and/or delta-tocopherol and/or other ingredients. In other preferred embodiments, the beta-tocopherol enriched tocopherol compositions of the present invention comprise additional. . .

DETD . . . at least 75% delta-tocopherol, at least 80% delta-tocopherol, at least 85% delta tocopherol, at least 90% delta-tocopherol, at least

95% **gamma-tocopherol** and at least 98% delta-tocopherol. Delta-tocopherol enriched tocopherol compositions comprise less than 50% alpha-tocopherol, less than 45% alpha-tocopherol, less than. . . and/or reduce cognitive dysfunction and may further comprise a delta-tocopherol metabolite and/or derivative and may further comprise alpha-tocopherol, beta-tocopherol and/or **gamma-tocopherol** and/or other ingredients. In other preferred embodiments, the delta-tocopherol enriched tocopherol compositions of the present invention comprise additional active ingredients,. . .

DETD [0025] Assays for measuring the effect of **gamma-tocopherol** enriched tocopherol compositions, beta-tocopherol enriched compositions and delta-tocopherol compositions are provided herein and are known to those of skill in. . .

DETD [0026] In other aspects the present invention provides **gamma-tocopherol** metabolite or derivative enriched compositions, beta-tocopherol metabolite or derivative enriched compositions, and delta-tocopherol metabolite or derivative enriched compositions, and methods for using such compositions. In preferred embodiments, the **gamma-tocopherol** metabolite, beta-tocopherol metabolite or delta-tocopherol metabolite enriched compositions of the present invention comprise at least 50% gamma-, beta-, or delta-tocopherol. . . least 90% gamma-, beta-, or delta-tocopherol metabolite or derivative and at least 95% gamma-, beta-, or delta-tocopherol metabolite or derivative. **Gamma-tocopherol**, beta-tocopherol or delta-tocopherol metabolite enriched compositions comprises less than 50% alpha-tocopherol, less than 45% alpha-tocopherol, less than 40% alpha-tocopherol, less. . . dysfunction. A gamma-, beta-, or delta-tocopherol metabolite or derivative enriched composition may further comprise tocopherol(s). In other preferred embodiments, the **gamma-tocopherol**, beta-tocopherol or delta-tocopherol metabolite or derivative enriched compositions of the present invention comprise additional active ingredients, and/or additional non-tocopherols. In. . .

DETD [0027] In illustrative embodiments disclosed herein a **gamma-tocopherol** enriched tocopherol composition and a **gamma-tocopherol** metabolite enriched composition are shown to reduce total infarct at the time of MCAO and at the time of reperfusion,. . .

DETD [0029] "**Cerebral Ischemia**" or "cerebral ischemic" or "a cerebral ischemic condition" refer to a medical event which is pathological in origin, or to. . . against and flattens the arteries and veins inside the brain, thereby reducing their ability to carry blood through the brain. **Cerebral ischemia** may also occur as a result of macro- or micro-emboli, such as may occur subsequent to cardiopulmonary bypass surgery.

DETD . . . and derivatives thereof) which are characterized by a 6-chromanol ring structure and a side chain at the 2 position. A "**gamma-tocopherol** enriched tocopherol composition", "beta-tocopherol enriched tocopherol composition" or a "delta-tocopherol enriched tocopherol composition" as used herein refers to the particular. . .

DETD [0033] **gamma-tocopherol**, 3,4-dihydro-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzyopyran-6-ol; 2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-6-chromanol; 7,8-dimethyltocol; o-xylotocopherol;

DETD . . . The term ".gamma.-CEHC" refers to the 2,7,8-trimethyl-2-(.beta.-carboxy-ethyl)-6-hydroxy chroman, having a molecular weight of 264. This compound is a metabolite of .**gamma.-tocopherol** and its synthesis and properties are described in U.S. Pat. No. 6,083,982, incorporated herein by reference (where it is also. . .

DETD [0042] By "**gamma-tocopherol** derivative" is meant **gamma.-tocopherol** metabolites and synthetic chroman derivatives including, but not limited to, .gamma.-CEHC, .gamma.-CEBC, racemic chromans, chroman methyl esters, chroman esters, chroman. . .

DETD . . . and benzodipyran methyl ester, as well as .gamma.-CEHC and .gamma.-CEBC, described above, and compounds shown in FIG. 3 herein. Other **gamma.-tocopherol** metabolites and synthetic

chroman derivatives may be known by those of skill in the art or will be discovered in. . .

DETD [0044] In the body of a subject, **gamma-tocopherol**, beta-tocopherol and delta-tocopherol break down into metabolites, including for example, the metabolites described in Wechter et al. U.S. Pat. Nos.. . . 6,150,402; 6,083,982; 6,048,891 and 6,242,479, specifically incorporated herein in their entirety. In particular, the present invention encompasses the use of **gamma-tocopherol** enriched tocopherol compositions that further comprise **gamma-tocopherol** metabolites such as gamma-CEHC, racemic gamma-CEHC and (S) gamma-CEHC. The general structure of other tocopherol metabolites are shown in FIG. 3. The present invention also encompasses the use of **gamma-tocopherol** metabolite enriched compositions that further comprise **gamma-tocopherol**.

DETD . . . compositions include without limitation, beta-tocopherol enriched tocopherol compositions, beta-tocopherol metabolite enriched compositions, delta-tocopherol enriched tocopherol compositions, delta-tocopherol metabolite enriched compositions, **gamma-tocopherol** enriched tocopherol compositions, **gamma-tocopherol** metabolite enriched compositions, epsilon-tocopherol enriched tocopherol compositions, zeta-tocopherol enriched tocopherol compositions, etc.

DETD . . . or "cytoprotective agents" are defined herein as compounds, mixtures, or formulations of compounds which are capable of preventing or treating **cerebral ischemia**, such as by reducing **neuronal damage** or symptoms thereof, associated with a cerebral ischemic condition and/or cell damage due to **cerebral ischemia**. "Amelioration" means the prevention, reduction, palliation, or a counter-acting of the negative aspects of an ischemic condition or ischemic state.. . .

DETD . . . symptoms of a cerebral ischemic condition and/or injury(ies) suffered by cells, tissues, organs and/or organisms that is induced secondary to **cerebral ischemia**. Cytoprotective activity and injury can be quantified in assays which measure results of injury such as death and inhibition of. . .

DETD [0055] By "amounts effective to reduce **neuronal damage** associated with a cerebral ischemic conditions and/or symptoms due to **cerebral ischemia**" is meant that the cytoprotective agent or agents (e.g., **gamma-tocopherol**, and/or beta-tocopherol, and/or delta tocopherol and/or a mixture thereof and/or derivatives and/or metabolites thereof) is present in a final concentration sufficient for reducing injury(ies) associated with a cerebral ischemic condition and/or symptoms due to **cerebral ischemia**. This amount includes, but is not limited to, a concentration which acts as a complete prophylaxis or treatment for a symptom of **neuronal damage**. An "effective amount" is an amount sufficient to effect beneficial or desired results. An effective amount can be administered in. . . least about 70%, even more preferably at least about 80%, and even more preferably at least about 90% reduction in **neuronal damage**.

DETD [0064] Provided herein are **gamma-tocopherol** enriched tocopherol compositions comprising **gamma-tocopherol** that may further comprise **gamma-tocopherol** metabolites, and/or **gamma-tocopherol** derivatives and/or other tocopherols, eg, beta- and delta-tocopherol, for use as cytoprotectants against damage, injury(ies) and/or symptoms associated with **cerebral ischemia**. Also provided herein are **gamma-tocopherol** metabolite enriched compositions comprising **gamma-tocopherol** metabolite(s) that may further comprise **gamma-tocopherol**, and/or derivatives thereof, and/or other tocopherol metabolites, for use as cytoprotectants against damage, injury(ies) and/or symptoms associated with **cerebral ischemia**.

DETD . . . and/or beta-tocopherol derivatives, and/or other tocopherols, eg, gamma- and delta-tocopherolfor use as cytoprotectants against damage, injury(ies) and/or symptoms associated with **cerebral**

ischemia. Also provided herein are beta-tocopherol metabolite enriched compositions comprising beta-tocopherol metabolite(s) that may further comprise beta-tocopherol, and/or derivatives thereof, and/or other tocopherol metabolites, for use as cytoprotectants against damage, injury(ies) and/or symptoms associated with **cerebral ischemia**.

DETD . . . delta-tocopherol derivatives, and/or other tocopherols, eg gamma- and beta-tocopherol, for use as cytoprotectants against damage, injury(ies) and/or symptoms associated with **cerebral ischemia**. Also provided herein are delta-tocopherol metabolite enriched compositions comprising delta-tocopherol metabolite(s) that may further comprise delta-tocopherol, and/or derivatives thereof, and/or other tocopherol metabolites, for use as cytoprotectants against damage, injury(ies) and/or symptoms associated with **cerebral ischemia**.

DETD [0067] These compounds are present in the compositions in amounts effective to ameliorate the injury(ies) and/or symptoms associated with **cerebral ischemia**. Preferably **gamma-tocopherol** enriched compositions comprise at least 50% **gamma-tocopherol**, at least 55% **gamma-tocopherol**, at least 60% **gamma-tocopherol**, at least 65% **gamma-tocopherol**, at least 70% **gamma-tocopherol**, at least 75% **gamma-tocopherol**, at least 80% **gamma-tocopherol**, at least 85% **gamma tocopherol**, at least 90% **gamma-tocopherol** and at least 95% **gamma-tocopherol**. **Gamma-tocopherol** enriched tocopherol compositions may also comprise **gamma-tocopherol** derivative(s) and/or **gamma tocopherol** metabolite(s), and/or other tocopherol(s) and/ or mixtures thereof. **Gamma-tocopherol** enriched tocopherol compositions comprises less than 50% alpha-tocopherol, less than 45% alpha-tocopherol, less than 40% alpha-tocopherol, less than 35% alpha-tocopherol,. . .

DETD [0068] Preferably, **gamma-tocopherol** metabolite enriched compositions comprise at least 50% **gamma-tocopherol** metabolite, at least 55% **gamma-tocopherol** metabolite, at least 60% **gamma-tocopherol** metabolite, at least 65% **gamma-tocopherol** metabolite, at least 70% **gamma-tocopherol** metabolite, at least 75% **gamma-tocopherol** metabolite, at least 80% **gamma-tocopherol** metabolite, at least 85% **gamma tocopherol** metabolite, at least 90% **gamma-tocopherol** metabolite and at least 95% **gamma-tocopherol** metabolite. In preferred embodiments, **gamma-tocopherol** metabolite enriched compositions comprises less than 50% alpha-tocopherol, less than 45% alpha-tocopherol, less than 40% alpha-tocopherol, less than 35% alpha-tocopherol,. . . than 25% alpha-tocopherol, less than 20% alpha-tocopherol, less than 15% alpha-tocopherol, less than 10% alpha-tocopherol or less than 5% alpha-tocopherol. **Gamma-tocopherol** metabolite enriched compositions may also comprise **gamma-tocopherol** and/or a **gamma tocopherol** derivative(s), and/or other tocopherol(s) and/ or mixtures thereof.

DETD [0073] In illustrative examples disclosed herein, a **gamma-tocopherol** enriched composition (obtained from Sigma and comprising greater than 97% **gamma-tocopherol**) and a **gamma-tocopherol** metabolite enriched composition, gamma-CEHC (greater than 98% gamma-CEHC) are able to reduce total infarct size when administered at the time. . . measured for various tocopherol containing compositions at MCAO and reperfusion as measured by the assay described in Example 2. A **gamma-tocopherol** enriched composition comprising greater than 97% **gamma-tocopherol** and administered IV at 6 mg/kg, at MCAO was able to reduce infarct size by 82% whereas an alpha-tocopherol containing. . . MCAO was able to reduce infarct by 42%. In additional

experiments it was shown that for administration at MCAO, a **gamma-tocopherol** enriched composition was able to reduce infarct size by 81% when administered IV at 0.60 mg/kg and a delta-tocopherol containing. . . to reduce infarct size by 52%. In additional experiments, it was shown that for administration at 3 hours pre-MCAO, a **gamma-tocopherol** enriched composition was able to reduce infarct size by 77% when administered by gavage at 10.00 mg/kg and a beta-tocopherol. . . at 10.00 mg/kg was able to reduce infarct size by 76%. It was also shown that gamma-CEHC enriched composition decreased **neuronal damage** by 50-65% in drug ranges 0.1-5 mg/kg when administered IV at MCAO.

DETD . . . by modifying the length of the side chain from that found in prototypical tocopherols such as alpha-, beta-, delta- and **gamma-tocopherol**. Tocopherols can also vary in stereochemistry and saturation of bonds in the ring structure and side chain. Additional tocopherol derivatives,. . .

DETD [0075] **Gamma-tocopherol** metabolites and derivatives are disclosed in Wechter et al., U.S. Pat. No. 6,150,402; 6,083,982 and 6,048,891. Other tocopherol metabolites or. . .

DETD [0091] Specific examples of **gamma-tocopherol** metabolites include for example, gamma-CEHC: synonyms: 6-hydroxy-2,7,8-trimethylchroman-2-propanoic acid and 2,7,8-trimethyl-2-(.beta.-carboxyethyl)-6-hydroxy chroman, and having formula: ##STR5##

DETD [0146] In preferred embodiments of the present invention, **gamma-tocopherol** enriched tocopherol compositions include for example:

DETD [0147] **gamma-tocopherol** enriched composition comprising greater than 90% **gamma-tocopherol** and more preferably greater than 95% **gamma-tocopherol**;

DETD [0149] **gamma-tocopherol** enriched composition comprising gamma-CEHC;

DETD [0150] **gamma-tocopherol** enriched composition for intravenous injection comprising at least 50% **gamma-tocopherol** and delta-tocopherol;

DETD [0151] **gamma-tocopherol** enriched composition for gavage administration comprising at least 50% **gamma-tocopherol** and beta-tocopherol;

DETD . . . include without limitation the use of hippocampal cell assay, animal cerebral infarct assay and animal assay for behavioral recovery after **cerebral ischemia**. Gamma-, beta-, or delta-tocopherol enriched tocopherol compositions and gamma-, beta-, or delta-tocopherol metabolite enriched compositions suitable for the present invention. . . condition, reduction in infarct size, reduction in cognitive disorder as measured by the methods disclosed in the Examples. Reduction in **neuronal damage** associated with a cerebral ischemic condition is quantified at least about 30%, preferably at least about 50%, more preferably at. . .

DETD [0155] It is well known that **gamma-tocopherol** is metabolized in vivo to form, for example, gamma-CEHC and gamma-CEBC, among other metabolites. In humans, this metabolite is thought. . .

DETD [0159] In one aspect, methods of the present invention relate to preventing **neuronal damage** in a mammalian subject at risk of developing injury due to a cerebral ischemic condition, e.g. for example, by an infarct in the brain. The methods of reducing **neuronal damage** relate to minimizing the extent and/or severity of injury in the brain associated with or due to a cerebral ischemic condition by ameliorating or reducing the injury that would otherwise occur. The methods encompass administering a **gamma-tocopherol** enriched tocopherol composition and/or a beta-tocopherol enriched tocopherol composition and/or a delta-tocopherol enriched tocopherol composition and/or a gamma-, beta-, or. . . subject. The amount administered and the duration of the treatment are effective to minimize the size and/or severity of the **neuronal damage** in the mammalian subject as measured by for example, reduction in neuronal cell death and/or reduction in tissue edema associated. . . in infarct size. Thus, it is anticipated

that as a result of such treatment the size and/or severity of any **neuronal damage** that develops is minimized.

DETD [0160] The present invention provides prophylactic treatments for **neuronal damage** including cell death and/or presence of tissue edema and/or cognitive dysfunction and/or cerebral infarcts which may be due to ischemic,. . . gamma-, beta-, or delta-tocopherol metabolite enriched compositions of the present invention are administered to a subject at risk of experiencing **neuronal damage** associated or due to a cerebral ischemic condition, and ameliorates the severity of the damage, should it occur. The method is intended for a subject at risk of **neuronal damage** that is associated with, or results from, an acute or chronic medical condition. Such conditions might arise as a result. . . emergent medical condition such as a stroke or severe blood loss. Other conditions which place a subject at risk for **neuronal damage** associated with a cerebral ischemic condition include a genetic predisposition to stroke or a condition that is understood to increase. . .

DETD [0161] Additional medical conditions that place a subject at risk for **neuronal damage** associated with or due to a cerebral ischemic condition include, but are not limited to, thrombosis; vasculitis (including collagen vascular. . .

DETD [0162] Medical conditions that place a subject at risk of **neuronal damage** associated with or due to a cerebral ischemic condition due to intracranial hemorrhage include, but are not limited to, spontaneous. . .

DETD . . . thereof, in an effective amount. With regard to a cerebral ischemic condition, an effective amount is one sufficient to reduce **neuronal damage** resulting from the cerebral ischemic condition. A reduction of **neuronal damage** is any prevention of injury to the brain which otherwise would have occurred in a subject experiencing a cerebral ischemic. . .

DETD . . . supplements may also be incorporated into food stuffs, such as, functional foods designed to promote cerebral health or to prevent **cerebral ischemia**. If administered as a medicinal preparation, the composition can be administered, either as a prophylaxis or treatment, to a patient. . .

DETD . . . and ex vivo use, a variety of concentrations may be used and various assays employed to determine the degree of **neuronal damage**, such as, for example, measurements of cell death, infarct size, and cognitive dysfunction.

DETD . . . enriched tocopherol compositions, and/or gamma-, beta-, or delta-tocopherol metabolite enriched compositions, and methods using the compositions are capable of reducing **neuronal damage** associated with **cerebral ischemia**. These conditions can be induced experimentally by chemical interference or by changing the environmental conditions in the laboratory (e.g., by. . .

DETD [0200] Various assays, compositions and methods useful for identifying compositions and methods for reducing **neuronal damage** are provided in the Examples.

DETD [0220] In experiments carried out in support of the invention, **gamma-tocopherol** enriched tocopherol compositions and gamma-CEHC enriched compositions each provided at least 40% protection against hippocampal cell injury in the primary. . .

DETD [0221] This assay is used to assess the efficacy of the test agents in protecting the brain against necrosis following **cerebral ischemia** induced in rats. Middle Cerebral Artery Occlusion (MCAO) is a widely used technique to induce transient focal **cerebral ischemia** in animal models. It has been demonstrated that the rat model of MCAO is an appropriate approximation of ischemic damage. . .

DETD [0226] The following is a description of various ways by which **gamma-tocopherol** enriched tocopherol compositions and **gamma-tocopherol** metabolite enriched compositions are administered in this assay.

DETD [0263] When **gamma-tocopherol** enriched tocopherol composition (greater than 90% **gamma-tocopherol**) was

administered I.V. at the time of MCAO, total infarct volume, total ischemic damage and cerebral edema were significantly reduced relative to that of control animals. Administration of the **gamma-tocopherol** metabolite, gamma-CEHC, I.V. at the time of MCAO also resulted in significantly reduced total infarct volume and total ischemic damage. . . . the time of MCAO also resulted in reduced cerebral edema relative to that of control animals. Thus, administration of a **gamma-tocopherol** enriched tocopherol composition or a **gamma-tocopherol** metabolite enriched composition provided protection to the brain against damage and effects associated with **cerebral ischemia**.

DETD [0264] Administration of a **gamma-tocopherol** enriched composition or a **gamma-tocopherol** metabolite enriched composition at the time of reperfusion resulted in reduction of total infarct volume, total ischemic damage and cerebral. . .

DETD [0265] The protective effects of alpha-tocopherol and delta-tocopherol were also assessed in the MCAO assay. At the same concentration, **gamma-tocopherol** was more effective in the reduction of total infarct volume and in the reduction of tissue edema than alpha-or. . .

DETD Animal Assay for Behavioral Recovery after **Cerebral Ischemia**

DETD [0266] This assay is used to assess the efficacy of the test agents in behavioral recovery after **cerebral ischemia** induced in rats. Clinical behavior evaluation includes neurological examination, sensomotor activity and learning and memory behavior testing.

CLM What is claimed is:

. . . comprising administering to the subject an effective amount of a non-alpha tocopherol enriched tocopherol composition, and by said administering, reducing **neuronal damage** related to said cerebral ischemic condition.

2. The method of claim 1 wherein the non-alpha tocopherol enriched tocopherol composition is a **gamma-tocopherol** enriched tocopherol composition.

3. The method of claim 1 wherein the non-alpha tocopherol enriched tocopherol composition is a **gamma-tocopherol** metabolite enriched composition.

8. The method of claim 3 wherein said **gamma-tocopherol** metabolite is gamma-CEHC.

11. The method of claim 1 wherein the **cerebral ischemia** is due to a spasm of the coronary vasculature.

15. The method of claim 2 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 60% **gamma-tocopherol**.

16. The method of claim 2 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 65% **gamma-tocopherol**.

17. The method of claim 2 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 70% **gamma-tocopherol**.

18. The method of claim 2 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 75% **gamma-tocopherol**.

19. The method of claim 2 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 80% **gamma-tocopherol**.

20. The method of claim 2 wherein said **gamma-**

tocopherol enriched tocopherol composition comprises at least 85% **gamma-tocopherol**.

21. The method of claim 2 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 90% **gamma-tocopherol**.

22. The method of claim 2 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 95% **gamma-tocopherol**.

23. The method of claim 2 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 98% **gamma-tocopherol**.

24. The method of claim 3 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 60% **gamma-tocopherol** metabolite.

25. The method of claim 3 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 65% **gamma-tocopherol** metabolite.

26. The method of claim 3 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 70% **gamma-tocopherol** metabolite.

27. The method of claim 3 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 75% **gamma-tocopherol** metabolite.

28. The method of claim 3 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 80% **gamma-tocopherol** metabolite.

29. The method of claim 3 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 85% **gamma-tocopherol** metabolite.

30. The method of claim 3 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 90% **gamma-tocopherol** metabolite.

31. The method of claim 3 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 95% **gamma-tocopherol** metabolite.

32. The method of claim 3 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 98% **gamma-tocopherol** metabolite.

L10 ANSWER 4 OF 7 USPATFULL
AN 2002:243654 USPATFULL
TI Compositions and methods for the prevention and treatment of tissue ischemia
IN Miller, Guy Michael, San Jose, CA, UNITED STATES
Brown, Lesley A., San Jose, CA, UNITED STATES
Del Balzo, Ughetta, Morgan Hill, CA, UNITED STATES
Flaim, Stephen, San Diego, CA, UNITED STATES
Boddupalli, Sekhar, San Jose, CA, UNITED STATES
Wang, Bing, Cupertino, CA, UNITED STATES
PI US 2002132845 A1 20020919
AI US 2001-17717 A1 20011214 (10)
PRAI US 2000-256269P 20001215 (60)
US 2001-296581P 20010606 (60)
US 2001-296580P 20010606 (60)

US 2001-343575P 20011019 (60)
DT Utility
FS APPLICATION
LREP Gladys H. Monroy, Morrison & Foerster LLP, 755 Page Mill Road, Palo Alto, CA, 94304-1018
CLMN Number of Claims: 97
ECL Exemplary Claim: 1
DRWN 7 Drawing Page(s)
LN.CNT 3908
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides compositions and methods for the treatment of tissue ischemia, and in particular, **cerebral ischemia**. In particular, the present invention provides gamma-, beta-, or delta-tocopherol enriched tocopherol compositions and gamma-, beta-, or delta-tocopherol metabolite enriched compositions and/or flavonoid enriched and/or a flavonoid derivative enriched compositions and methods for their use in preventing or treating a tissue ischemic condition or a cerebral ischemic condition. The present invention also provides pharmaceutical compositions comprising gamma-, beta-, or delta-tocopherol enriched tocopherol composition, a gamma-, beta-, or delta-tocopherol metabolite enriched compositions or flavonoid enriched compositions or flavonoid derivative enriched compositions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides compositions and methods for the treatment of tissue ischemia, and in particular, **cerebral ischemia**. In particular, the present invention provides gamma-, beta-, or delta-tocopherol enriched tocopherol compositions and gamma-, beta-, or delta-tocopherol metabolite enriched. . .
SUMM [0002] This invention generally relates to compositions and methods comprising **gamma-tocopherol** and/or a metabolite and/or a derivative thereof; beta-tocopherol and/or a metabolite and/or a derivative thereof; delta-tocopherol and/or a metabolite and/or. . .
SUMM [0003] Ischemia may be defined as the loss of blood flow to a tissue. **Cerebral ischemia**, also known as stroke, is the interruption or reduction of blood flow in the arteries feeding the brain. Loss of. . .
SUMM . . . Res. Comm. Mol. Pathol. Pharmacol. 101:259-268; Gebicki et al. (1999) Biochem. J. 338:629-636. ROS are also produced in response to **cerebral ischemia**, including that caused by stroke, traumatic head injury and spinal injury. In addition, when metabolism increases or a body is. . .
SUMM . . . 1501S-1509S. Alpha-tocopherol also functions as a scavenger of active nitrogen species (Halliwell et al. (1992) FEBS Lett. 313:62-66) and a **gamma-tocopherol** metabolite is an alleged natriuretic (Wechter et al. (1996) Proc. Natl. Acad. Sci. USA 93:6002-6007). See also U.S. Pat. Nos. 6,150,402; 6,083,982; 6,048,891, and 6,242,479. Alpha-tocopherol has been alleged to have an effect on **cerebral ischemia**. Yamamoto et al., 1983, Stroke, vol. 14:977-982; Hara et al., 1990, Brain Research, vol. 510: 335-338; and Altura, et al.,. . .
SUMM . . . in a mammalian subject. The present invention also relates to compositions and methods for treating and/or ameliorating the symptoms of **cerebral ischemia** in a mammalian subject. Accordingly, the present invention provides methods for treating and/or ameliorating the symptoms of a cerebral ischemic. . . comprising administering to the subject an effective amount of a non-alpha tocopherol enriched tocopherol composition, and by said administering, reducing **neuronal damage** related to said cerebral ischemic condition. In some embodiments, the non-alpha tocopherol enriched tocopherol composition is a **gamma-tocopherol** enriched tocopherol composition. In additional embodiments, the non-alpha tocopherol is a **gamma-tocopherol** metabolite enriched composition. In other embodiments, the non-alpha tocopherol enriched tocopherol composition is a beta-tocopherol enriched tocopherol composition. In further. . . 1 to about 50 mg per kg body weight of said mammalian subject. In other aspects the present invention

provides **gamma-tocopherol** enriched tocopherol compositions comprising **gamma tocopherol** in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition. In further embodiments, the present invention provides beta-tocopherol enriched tocopherol compositions comprising beta tocopherol in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition. In yet further embodiments, the present invention provides delta-tocopherol enriched tocopherol compositions comprising delta tocopherol in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition.

SUMM . . . related to said tissue ischemic condition. In some embodiments, the tissue ischemic condition is selected from the group consisting of **cerebral ischemia**; intestinal ischemia; spinal cord ischemia; cardiovascular ischemia; myocardial ischemia associated with myocardial infarction; mycardial ischemia associated with CHF, ischemia associated. . . gangrenous conditions, post-trauma syndrome, cardiac arrest resuscitation, peripheral nerve damage or neuropathies. In some embodiments, the tissue ischemic condition is **cerebral ischemia**. In further embodiments, a composition comprises a beta-tocopherol in a range of about 1 to about 1000 mg per kg. . .

SUMM . . . related to said tissue ischemic condition. In some embodiments, the tissue ischemic condition is selected from the group consisting of **cerebral ischemia**; intestinal ischemia; spinal cord ischemia; cardiovascular ischemia; myocardial ischemia associated with myocardial infarction; mycardial ischemia associated with CHF, ischemia associated. . . gangrenous conditions, post-trauma syndrome, cardiac arrest resuscitation, peripheral nerve damage or neuropathies. In further embodiments, the tissue ischemic condition is **cerebral ischemia**. In further embodiments, a composition comprises a delta-tocopherol in a range of about 1 to about 1000 mg per kg. . .

SUMM . . . of a non-cardiovascular tissue ischemic condition in a mammalian subject, comprising administering to the subject an effective amount of a **gamma-tocopherol** enriched tocopherol composition, and by said administering, reducing tissue damage related to said non-cardiovascular tissue ischemic condition. The present invention. . . of a non-cardiovascular tissue ischemic condition in a mammalian subject, comprising administering to the subject an effective amount of a **gamma-tocopherol** metabolite enriched composition, and by said administering, reducing tissue damage related to said non-cardiovascular tissue ischemic condition. In some embodiments,. . . ischemia associated with diabetic ulcers, gangrenous conditions, post-trauma syndrome, peripheral nerve damage or neuropathies. In some embodiments, a composition comprises **gamma -tocopherol** in a range of about 1 to about 1000 mg per kg body weight of said mammalian subject. In further embodiments, a composition comprises **gamma-tocopherol** in a range of about 1 to about 50 mg per kg body weight of said mammalian subject. In yet additional embodiments, a composition comprises **gamma-tocopherol** in a range of about 10 to about 100 mg per kg body weight of said mammalian subject.

SUMM . . . by said administering, reducing tissue damage related to said tissue ischemic condition. In some embodiments, the tissue ischemic condition is **cerebral ischemia**. In other embodiments, the tissue ischemic condition is cardiovascular ischemia. In further embodiments, the non-alpha tocopherol is selected from the group consisting of **gamma-tocopherol**, beta-tocopherol, delta-tocopherol, a **gamma-tocopherol** metabolite, a beta-tocopherol metabolite, and a delta-tocopherol metabolite. In further embodiments, the non-alpha tocopherol is **gamma-tocopherol**. In yet additional embodiments, the non-alpha-tocopherol is a **gamma-tocopherol** metabolite. In further embodiments, the composition comprises **gamma-tocopherol** and two flavonoids. In yet further embodiments, the composition comprises **gamma-tocopherol**, quercetin and hesperetin. In yet additional embodiments, the flavonoid is metal chelated. In some embodiments, the

composition comprises **gamma-tocopherol** in the range of about 1 to about 1000 mg/kg body weight of mammalian subject, hesperetin in the range of. . . range of about 1 to about 1000 mg/kg body weight of mammalian subject. In yet additional embodiments, the composition comprises **gamma-tocopherol** in the range of about 1 to about 50 mg/kg body weight of mammalian subject, hesperetin in the range of. . . a range of about 1 to about 25 mg/kg body weight of mammalian subject. In further embodiments, the composition comprises **gamma-tocopherol** in the range of about 10 to about 100 mg/kg body weight of mammalian subject, hesperetin in the range of. . .

SUMM [0021] In some aspects of the present invention, a **gamma tocopherol** enriched tocopherol composition comprises at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% **gamma-tocopherol**, or at least 98% **gamma -tocopherol**. In other aspects, a beta-tocopherol enriched tocopherol composition comprises at least 50%, at least 60%, at least 70%, at least. . . 70%, at least 80%, at least 90%, at least 95% delta-tocopherol, or at least 98% delta-tocopherol. In further aspects, a **gamma tocopherol** metabolite enriched composition comprises at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 98% **gamma-tocopherol** metabolite. In some embodiments, the **gamma-tocopherol** metabolite is gamma-CEHC. In other aspects, a beta-tocopherol metabolite enriched composition comprises at least 50%, at least 60%, at least. . .

SUMM [0022] The present invention also provides compositions comprising a non-alpha tocopherol and a flavonoid in amounts effective to reduce **neuronal damage** related to a cerebral ischemic condition. In some embodiments, the composition comprises hesperetin or quercetin. In other embodiments, the composition comprises **gamma -tocopherol**, hesperetin or quercetin. In yet further embodiments, the composition comprises diosmin and **gamma-tocopherol**. In yet further embodiments, the composition comprises delta-tocopherol and hesperetin. In yet further embodiments, the composition comprises **gamma-tocopherol** and biochanin A.

DRWD [0024] FIG. 1 shows the effect of **gamma-tocopherol** and its metabolite, gamma-carboxy ethyl hydroxy chroman (gamma-CEHC), on the volumetric comparison of total infarct with administration of **gamma-tocopherol** and gamma-CEHC at the time of Middle Cerebral Artery Occlusion (MCAO) as described in Example 2.

DRWD [0025] FIG. 2 shows the effect of **gamma-tocopherol** and its metabolite, gamma-CEHC, on the volumetric comparison of total infarct with administration of **gamma-tocopherol** and gamma-CEHC at reperfusion as described in Example 2.

DRWD [0028] FIG. 5 shows the effect of **gamma-tocopherol** on stroke protection as measured in a **cerebral ischemia** MCAO model.

DETD . . . of naturally-occurring compounds that can be used in nutritional and pharmaceutical compositions that are protective in tissue ischemia, such as **cerebral ischemia** (stroke) and mycardial injury subsequent to ischemia or hypoxia. The present invention provides compositions and methods for treating and/or ameliorating the symptoms of tissue ischemia, such as for example, **cerebral ischemia**, cardiovascular ischemia, spinal cord ischemia, intestinal ischemia, liver ischemia, kidney ischemia, dermal ischemia, and other tissue ischemias by for example. . . size associated with myocardial ischemia. The present invention also provides compositions and methods for treating and/or ameliorating the symptoms of **cerebral ischemia**, such as for example, by reducing neuronal cell death, reducing tissue edema, and/or reducing cognitive dysfunction associated with a cerebral. . .

DETD [0032] The present invention provides **gamma-tocopherol** enriched tocopherol compositions, beta-tocopherol enriched tocopherol compositions and delta-tocopherol enriched compositions and methods for using such compositions. In preferred embodiments, **gamma-**

tocopherol enriched tocopherol compositions of the present invention comprise at least 50% **gamma-tocopherol**, at least 55% **gamma-tocopherol**, at least 60% **gamma-tocopherol**, at least 65% **gamma-tocopherol**, at least 70% **gamma-tocopherol**, at least 75% **gamma-tocopherol**, at least 80% **gamma-tocopherol**, at least 85% **gamma tocopherol**, at least 90% **gamma-tocopherol** and at least 95% **gamma-tocopherol**. **Gamma-tocopherol** enriched tocopherol compositions comprise less than 50% alpha-tocopherol, less than 45% alpha-tocopherol, less than 40% alpha-tocopherol, less than 35% alpha-tocopherol,. . . than 20% alpha-tocopherol, less than 15% alpha-tocopherol, less than 10% alpha-tocopherol or less than 5% alpha-tocopherol. In some embodiments, a **gamma-tocopherol** "enriched" tocopherol composition comprises **gamma-tocopherol** as the sole active ingredient. As used herein, an "active ingredient" is one that is able to treat and/or prevent. . . an amount effective to reduce cell death, reduce infarct size, reduce tissue edema associated with the ischemic condition, and/or in **cerebral ischemia**, reduce cognitive dysfunction and may further comprise a **gamma-tocopherol** metabolite and/or derivative and may further comprise additional tocopherols and/or other ingredients.

DETD [0033] In other embodiments, the **gamma-tocopherol** enriched tocopherol compositions of the present invention comprise additional active ingredients, and/or additional non-tocopherols. In some embodiments of **gamma-tocopherol** enriched tocopherol compositions, the **gamma-tocopherol** and additional ingredient(s) provide a synergistic effect. **Gamma-tocopherol** and an additional ingredient are considered to be synergistic when their combined effect is greater than additive of the individual. . . tocopherol and a flavonoid selected from the group hesperetin, quercetin, diosmin and biochanin A. In other embodiments, the composition comprises **gamma-tocopherol**, hesperetin or quercetin. In yet further embodiments, the composition comprises diosmin and **gamma-tocopherol**. In yet further embodiments, the composition comprises delta -tocopherol and hesperetin. In yet further embodiments, the composition comprises **gamma-tocopherol** and biochanin A.

DETD . . . cell death, reduce infarct size, reduce tissue edema associated with the ischemic condition, and/or reduce cognitive dysfunction, such as in **cerebral ischemia** and may further comprise a beta-tocopherol metabolite and/or derivative and may further comprise additional tocopherols and/or other ingredients. In other. . .

DETD . . . cell death, reduce infarct size, reduce tissue edema associated with the ischemic condition, and/or reduce cognitive dysfunction, such as for **cerebral ischemia** and may further comprise a delta-tocopherol metabolite and/or derivative and may further comprise additional tocopherols and/or other ingredients. In other. . .

DETD [0036] Assays for measuring the effect of **gamma-tocopherol** enriched tocopherol compositions, beta-tocopherol enriched compositions and delta-tocopherol compositions are provided herein and are known to those of skill in. . .

DETD [0037] In other aspects, the present invention provides **gamma-tocopherol** metabolite or derivative enriched compositions, beta-tocopherol metabolite or derivative enriched compositions, delta-tocopherol metabolite or derivative enriched compositions, and flavonoid enriched compositions, and methods for using such compositions. In preferred embodiments, the **gamma-tocopherol**, beta-tocopherol or delta-tocopherol metabolite enriched compositions of the present invention comprise at least 50% gamma-, beta-, or delta-tocopherol metabolite or. . . least 90% gamma-, beta-, or delta-tocopherol metabolite or derivative and at least 95% gamma-, beta-, or delta-tocopherol metabolite or derivative. **Gamma-tocopherol**, beta-tocopherol or delta-tocopherol metabolite enriched compositions comprises less than 50% alpha-tocopherol, less than 45% alpha-tocopherol, less than 40%

alpha-tocopherol, less. . . cell death, reduce infarct size, reduce tissue edema associated with the ischemic condition, and/or reduce cognitive dysfunction, such as in **cerebral ischemia**.
A gamma-, beta-, or delta-tocopherol metabolite or derivative enriched composition may further comprise tocopherol(s). In other preferred embodiments, the **gamma-tocopherol**, beta-tocopherol or delta-tocopherol metabolite or derivative enriched compositions of the present invention comprise additional active ingredients, and/or additional non-tocopherols. In. . .

DETD [0038] In illustrative embodiments disclosed herein a **gamma-tocopherol** enriched tocopherol composition and a **gamma-tocopherol** metabolite enriched composition are shown to reduce total infarct at the time of MCAO and at the time of reperfusion,. . .

DETD . . . a region of the tissue is impeded or blocked, either temporarily, as in vasospasm or transient ischemic attach (TIA) in **cerebral ischemia** or permanently, as in thrombolic occlusion in **cerebral ischemia**. The affected region is deprived of oxygen and nutrients as a consequence of the ischemic event. This deprivation leads to the injuries of infarction or in the region affected. The present invention encompasses **cerebral ischemia**; intestinal ischemia; spinal cord ischemia; cardiovascular ischemia; ischemia associated with CHF, liver ischemia; kidney ischemia; dermal ischemia; vasoconstriction-induced tissue ischemia,. . . against and flattens the arteries and veins inside the tissue, thereby reducing their ability to carry blood through the tissue. **Cerebral ischemia** may also occur as a result of macro-or micro-emboli, such as may occur subsequent to cardiopulmonary bypass surgery. Age-related macular. . .

DETD [0041] "**Cerebral Ischemia**" or "cerebral ischemic" or "a cerebral ischemic condition" refer to a medical event which is pathological in origin, or to. . . against and flattens the arteries and veins inside the brain, thereby reducing their ability to carry blood through the brain. **Cerebral ischemia** may also occur as a result of macro-or micro-emboli, such as may occur subsequent to cardiopulmonary bypass surgery.

DETD . . . and derivatives thereof) which are characterized by a 6-chromanol ring structure and a side chain at the 2 position. A "**gamma-tocopherol** enriched tocopherol composition", "beta-tocopherol enriched tocopherol composition" or a "delta-tocopherol enriched tocopherol composition" as used herein refers to the particular. . .

DETD [0045] **gamma-tocopherol**, 3,4-dihydro-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzyopyran-6-ol; 2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-6-chromanol; 7,8-dimethyltocol; o-xylotocopherol;

DETD . . . The term ".gamma.-CEHC" refers to the 2,7,8-trimethyl-2-(.beta.-carboxy-ethyl)-6-hydroxy chroman, having a molecular weight of 264. This compound is a metabolite of **.gamma.-tocopherol** and its synthesis and properties are described in U.S. Pat. No. 6,083,982, incorporated herein by reference (where it is also. . .

DETD [0054] By "**gamma-tocopherol** derivative" is meant **gamma.-tocopherol** metabolites and synthetic chroman derivatives including, but not limited to, .gamma.-CEHC, .gamma.-CEBC, racemic chromans, chroman methyl esters, chroman esters, chroman. . .

DETD . . . and benzodipyran methyl ester, as well as .gamma.-CEHC and .gamma.-CEBC, described above, and compounds shown in FIG. 3 herein. Other **gamma.-tocopherol** metabolites and synthetic chroman derivatives may be known by those of skill in the art or will be discovered in. . .

DETD [0056] In the body of a subject, **gamma-tocopherol**, beta-tocopherol and delta-tocopherol break down into metabolites, including for example, the metabolites described in Wechter et al. U.S. Pat. Nos.. . . 6,150,402; 6,083,982; 6,048,891 and 6,242,479, specifically incorporated herein in their entirety. In particular, the present invention encompasses the use of **gamma-tocopherol** enriched tocopherol compositions that further

comprise **gamma-tocopherol** metabolites such as gamma-CEHC, racemic gamma-CEHC and (S) gamma-CEHC. The general structure of other tocopherol metabolites are shown in FIG.. . .

DETD . . . compositions include without limitation, beta-tocopherol enriched tocopherol compositions, beta-tocopherol metabolite enriched compositions, delta-tocopherol enriched tocopherol compositions, delta-tocopherol metabolite enriched compositions, **gamma-tocopherol** enriched tocopherol compositions, **gamma-tocopherol** metabolite enriched compositions, epsilon-tocopherol enriched tocopherol compositions, zeta-tocopherol enriched tocopherol compositions, etc. By a "non-**gamma**" **tocopherol** enriched composition is meant a composition that is enriched in a tocopherol other than **gamma-tocopherol**. Examples of non-**gamma tocopherol** enriched tocopherol compositions include without limitation, beta-tocopherol enriched tocopherol compositions, beta-tocopherol metabolite enriched compositions, delta-tocopherol enriched tocopherol compositions, delta-tocopherol metabolite enriched compositions, **gamma-tocopherol** enriched tocopherol compositions, **gamma-tocopherol** metabolite enriched compositions, epsilon-tocopherol enriched tocopherol compositions, zeta-tocopherol enriched tocopherol compositions, etc. A non-alpha, non-**gamma-tocopherol** enriched tocopherol composition refers to a composition that is enriched in a tocopherol other than alpha-tocopherol and **gamma-tocopherol**. Examples of non-alpha, non-**gamma-tocopherol** enriched tocopherol compositions include without limitation, beta-tocopherol enriched tocopherol compositions, beta-tocopherol metabolite enriched compositions, delta-tocopherol enriched tocopherol compositions, delta-tocopherol metabolite enriched compositions, **gamma-tocopherol** enriched tocopherol compositions, **gamma-tocopherol** metabolite enriched compositions, epsilon-tocopherol enriched tocopherol compositions, zeta-tocopherol enriched tocopherol compositions, etc.

DETD . . . compounds, mixtures, or formulations of compounds which are capable of preventing or treating a tissue ischemia, such as for example, **cerebral ischemia**, such as by reducing tissue or cell damage or symptoms thereof, associated with an ischemic condition and/or cell damage due. . .

DETD . . . with a tissue ischemic conditions and/or symptoms due to tissue ischemia" is meant that the cytoprotective agent or agents (e.g., **gamma-tocopherol**, and/or beta-tocopherol, and/or delta tocopherol and/or a mixture thereof and/or derivatives and/or metabolites thereof and/or a flavonoid and/or derivatives thereof). . . a concentration which acts as a complete prophylaxis or treatment for a symptom of cellular or tissue damage, such as **neuronal damage** for **cerebral ischemia**. An "effective amount" is an amount sufficient to effect beneficial or desired results. An effective amount can be administered in. . . a tissue ischemic condition, the size and/or severity of an infarct in the tissue, such as in the brain for **cerebral ischemia**, of the subject may be determined, for example, by various noninvasive radiological procedures and/or by various symptomatic and diagnostic procedures. . . more preferably at least about 80%, and even more preferably at least about 90% reduction in tissue damage, such as **neuronal damage** for **cerebral ischemia**.

DETD . . . other tocopherols for use as cytoprotectants against damage, injury(ies) and/or symptoms associated with an ischemic condition. Also provided herein are **gamma-tocopherol** enriched tocopherol compositions comprising **gamma-tocopherol** that may further comprise **gamma-tocopherol** metabolites, and/or derivatives thereof, and/or other tocopherol metabolites, for use as cytoprotectants against damage, injury(ies) and/or symptoms associated with **cerebral ischemia**.

DETD [0088] Also provided herein are **gamma-tocopherol** metabolite enriched compositions comprising **gamma-tocopherol** metabolite(s) that may further comprise **gamma-tocopherol**, and/or derivatives thereof, and/or other

tocopherol metabolites, for use as cytoprotectants against damage, injury(ies) and/or symptoms associated with **cerebral ischemia**.

DETD [0091] Provided herein are flavonoid enriched compositions and flavonoid derivative enriched compositions and compositions comprising **gamma-tocopherol** and a flavonoid for use as cytoprotectants against damage, injury(ies) and/or symptoms associated with **cerebral ischemia**.

DETD . . . present in the compositions in amounts effective to ameliorate the injury(ies) and/or symptoms associated with a tissue ischemia, such as **cerebral ischemia**. Preferably **gamma-tocopherol** enriched compositions comprise at least 50% **gamma-tocopherol**, at least 55% **gamma-tocopherol**, at least 60% **gamma-tocopherol**, at least 65% **gamma-tocopherol**, at least 70% **gamma-tocopherol**, at least 75% **gamma-tocopherol**, at least 80% **gamma-tocopherol**, at least 85% **gamma tocopherol**, at least 90% **gamma-tocopherol** and at least 95% **gamma-tocopherol**. **Gamma-tocopherol** enriched tocopherol compositions may also comprise **gamma-tocopherol** derivative(s) and/or **gamma tocopherol** metabolite(s), and/or other tocopherol(s) and/or mixtures thereof. **Gamma-tocopherol** enriched tocopherol compositions comprises less than 50% alpha-tocopherol, less than 45% alpha-tocopherol, less than 40% alpha-tocopherol, less than 35% alpha-tocopherol,. . .

DETD [0093] Preferably, **gamma-tocopherol** metabolite enriched compositions comprise at least 50% **gamma-tocopherol** metabolite, at least 55% **gamma-tocopherol** metabolite, at least 60% **gamma-tocopherol** metabolite, at least 65% **gamma-tocopherol** metabolite, at least 70% **gamma-tocopherol** metabolite, at least 75% **gamma-tocopherol** metabolite, at least 80% **gamma-tocopherol** metabolite, at least 85% **gamma tocopherol** metabolite, at least 90% **gamma-tocopherol** metabolite and at least 95% **gamma-tocopherol** metabolite. In preferred embodiments, **gamma-tocopherol** metabolite enriched compositions comprises less than 50% alpha-tocopherol, less than 45% alpha-tocopherol, less than 40% alpha-tocopherol, less than 35% alpha-tocopherol,. . . than 25% alpha-tocopherol, less than 20% alpha-tocopherol, less than 15% alpha-tocopherol, less than 10% alpha-tocopherol or less than 5% alpha-tocopherol. **Gamma-tocopherol** metabolite enriched compositions may also comprise **gamma-tocopherol** and/or a **gamma tocopherol** derivative(s), and/or other tocopherol(s) and/or mixtures thereof.

DETD [0098] In illustrative examples disclosed herein, a **gamma-tocopherol** enriched composition (obtained from Sigma and comprising greater than 97% **gamma-tocopherol**) and a **gamma-tocopherol** metabolite enriched composition, gamma-CEHC (greater than 98% gamma-CEHC) are able to reduce total infarct size in an animal model of **cerebral ischemia**, the middle cerebral artery occlusion (MCAO model), when administered at the time of MCAO and when administered at reperfusion (see. . . was measured for various tocopherol containing compositions at before, during MCAO and at reperfusion as described in Example 2. A **gamma-tocopherol** enriched composition comprising greater than 97% **gamma-tocopherol** and administered IV at 0.6 and 6 mg/kg at MCAO reduced infarct size by 81% and 82%, respectively, whereas an. . . at 0.60 mg/kg was able to reduce infarct size by 52%. It was also shown that gamma-CEHC enriched composition decreased **neuronal damage** by 50-65% in drug ranges 0.1-5 mg/kg when administered IV at MCAO.

DETD . . . In further experiments in support of the present invention, test compounds were administered at reperfusion, as described in Example

2. **Gamma-tocopherol** (10 mg/kg) administration resulted in a reduction of infarct volume by 70%, while gamma-CEHC (10 mg/kg) administration resulted in a. . .

DETD . . . additional experiments carried out in support of the present invention, it was shown that when administered 3 hours pre-MCAO, a **gamma-tocopherol** enriched composition was able to reduce infarct size by 53% and 77%, respectively, when administered by oral gavage at 4. . .

DETD . . . conducted in which compound was administered intraperitoneally in the MCAO animal model described in Example 2. In an exemplary study, **gamma-tocopherol** (90% **gamma-tocopherol**, Sigma) administered at 10-20 mg/kg, either at MCAO or 3 hours post-reperfusion resulted in mean reduction of infarct volumes in. . .

DETD . . . with flavonoid compounds, as described herein. In an exemplary experiment, when administered by oral gavage 3 hours pre-MCAO, 4 mg/kg **gamma-tocopherol** produced a 53% reduction in infarct volume, while 6 mg/kg quercetin+hesperetin resulted in 38% reduction of infarct volume. Combination of these compounds (4 mg/kg **gamma-tocopherol** and 6 mg/kg quercetin+hesperetin) resulted in 73% reduction in infarct volume.

DETD . . . weight after intervention (drug treatment) indicates improvement. In experiments carried out in support of the present invention, intervention with a **gamma-tocopherol** enriched composition (>65% **gamma-tocopherol**) resulted in reduction in heart weight with no decrease in left ventricular systolic pressure (LVSP). By way of comparison, captopril. . .

DETD . . . by modifying the length of the side chain from that found in prototypical tocopherols such as alpha-, beta-, delta- and **gamma-tocopherol**. Tocopherols can also vary in stereochemistry and saturation of bonds in the ring structure and side chain. Additional tocopherol derivatives,. . .

DETD [0107] **Gamma-tocopherol** metabolites and derivatives are disclosed in Wechter et al., U.S. Pat. Nos. 6,150,402; 6,083,982 and 6,048,891. Other tocopherol metabolites or. . .

DETD [0122] Specific examples of **gamma-tocopherol** metabolites include for example, gamma-CEHC: synonyms: 6-hydroxy-2,7,8-trimethylchroman-2-propanoic acid and 2,7,8-trimethyl-2-(.beta.-carboxyethyl)-6-hydroxy chroman, and having formula: ##STR5##

DETD [0169] In experiments performed in support of the present invention, hesperetin was shown to act synergistically with **gamma-tocopherol** and delta-tocopherol.

DETD [0176] **gamma-tocopherol** enriched composition comprising greater than 90% **gamma-tocopherol** and more preferably greater than 95% **gamma-tocopherol**;

DETD [0178] **gamma-tocopherol** enriched composition comprising gamma-CEHC;

DETD [0179] **gamma-tocopherol** enriched composition for intravenous injection comprising at least 50% **gamma-tocopherol** and delta-tocopherol;

DETD [0180] **gamma-tocopherol** enriched composition for gavage administration comprising at least 50% **gamma-tocopherol** and beta-tocopherol;

DETD . . . include without limitation the use of hippocampal cell assay, animal cerebral infarct assay and animal assay for behavioral recovery after **cerebral ischemia**, and congestive heart failure model (CHF). Gamma-, beta-, or delta-tocopherol enriched tocopherol compositions and gamma-, beta-, or delta-tocopherol metabolite enriched. . . reduction in tissue edema associated with an ischemic condition, reduction in infarct size, reduction in cognitive disorder, such as in **cerebral ischemia**, as measured by the methods disclosed in the Examples. Reduction in cellular or tissue damage associated with a ischemic condition. . . more preferably at least about 80%, and even more preferably at least about 90% reduction. It is well known that **gamma-tocopherol**

is metabolized in vivo to form, for example, gamma-CEHC and gamma-CEBC, among other metabolites. In humans, this metabolite is thought. . .

DETD [0185] compositions comprising **gamma-tocopherol**, hesperetin and quercetin;

DETD [0194] In the present invention, the ranges of the components of a composition disclosed above, such as for example, **gamma-tocopherol**, hesperetin and quercetin or bromo-quercetin can be selected from any of the ranges given for the individual components. In one. . .

DETD [0198] In one aspect, methods of the present invention relate to preventing **neuronal damage** in a mammalian subject at risk of developing injury due to a cerebral ischemic condition, e.g. for example, by an infarct in the brain. The methods of reducing **neuronal damage** relate to minimizing the extent and/or severity of injury in the brain associated with or due to a cerebral ischemic. . . by ameliorating or reducing the injury that would otherwise occur. The methods encompass administering a non-alpha tocopherol, such as, a **gamma-tocopherol** enriched tocopherol composition and/or a beta-tocopherol enriched tocopherol composition and/or a delta-tocopherol enriched tocopherol composition and/or a gamma-, beta-, or. . . subject. The amount administered and the duration of the treatment are effective to minimize the size and/or severity of the **neuronal damage** in the mammalian subject as measured by for example, reduction in neuronal cell death and/or reduction in cerebral edema associated. . . in infarct size. Thus, it is anticipated that as a result of such treatment the size and/or severity of any **neuronal damage** that develops is minimized.

DETD [0199] The present invention provides prophylactic treatments for **neuronal damage** including cell death and/or presence of tissue edema and/or cognitive dysfunction and/or cerebral infarcts which may be due to ischemic,. . . flavonoid enriched and/or flavonoid derivative enriched compositions of the present invention are administered to a subject at risk of experiencing **neuronal damage** associated or due to a cerebral ischemic condition, and ameliorates the severity of the damage, should it occur. The method is intended for a subject at risk of **neuronal damage** that is associated with, or results from, an acute or chronic medical condition. Such conditions might arise as a result. . . emergent medical condition such as a stroke or severe blood loss. Other conditions which place a subject at risk for **neuronal damage** associated with a cerebral ischemic condition include a genetic predisposition to stroke or a condition that is understood to increase. . .

DETD [0200] Additional medical conditions that place a subject at risk for **neuronal damage** associated with or due to a cerebral ischemic condition include, but are not limited to, thrombosis; vasculitis (including collagen vascular. . .

DETD [0201] Medical conditions that place a subject at risk of **neuronal damage** associated with or due to a cerebral ischemic condition due to intracranial hemorrhage include, but are not limited to, spontaneous. . .

DETD . . . to an intestinal ischemic condition by ameliorating or reducing the injury that would otherwise occur. The methods encompass administering a **gamma-tocopherol** enriched tocopherol composition and/or a beta-tocopherol enriched tocopherol composition and/or a delta-tocopherol enriched tocopherol composition and/or a gamma-, beta-, or. . .

DETD . . . an spinal cord ischemic condition by ameliorating or reducing the injury that would otherwise occur. The methods encompass administering a **gamma-tocopherol** enriched tocopherol composition and/or a beta-tocopherol enriched tocopherol composition and/or a delta-tocopherol enriched tocopherol composition and/or a gamma-, beta-, or. . .

DETD . . . composition in an effective amount. With regard to a cerebral ischemic condition, an effective amount is one sufficient to reduce **neuronal damage** resulting from the cerebral ischemic

condition. A reduction of **neuronal damage** is any prevention of injury to the brain which otherwise would have occurred in a subject experiencing a cerebral ischemic. . .

DETD . . . supplements may also be incorporated into food stuffs, such as, functional foods designed to promote cerebral health or to prevent **cerebral ischemia**. If administered as a medicinal preparation, the composition can be administered, either as a prophylaxis or treatment, to a patient. . .

DETD . . . and ex vivo use, a variety of concentrations may be used and various assays employed to determine the degree of **neuronal damage**, such as, for example, measurements of cell death, infarct size, and cognitive dysfunction.

DETD . . . enriched tocopherol compositions, and/or gamma-, beta-, or delta-tocopherol metabolite enriched compositions, and methods using the compositions are capable of reducing **neuronal damage** associated with **cerebral ischemia**. These conditions can be induced experimentally by chemical interference or by changing the environmental conditions in the laboratory (e.g., by. . .

DETD [0246] Various assays, compositions and methods useful for identifying compositions and methods for reducing **neuronal damage** are provided in the Examples.

DETD [0266] In experiments carried out in support of the invention, **gamma-tocopherol** enriched tocopherol compositions and gamma-CEHC enriched compositions each provided at least 40% protection against hippocampal cell injury in the primary. . .

DETD [0267] This assay is used to assess the efficacy of the test agents in protecting the brain against necrosis following **cerebral ischemia** induced in rats. Middle Cerebral Artery Occlusion (MCAO) is a widely used technique to induce transient focal **cerebral ischemia** in animal models. It has been demonstrated that the rat model of MCAO is an appropriate approximation of ischemic damage. . .

DETD [0272] The following is a description of various ways by which **gamma-tocopherol** enriched tocopherol compositions and **gamma-tocopherol** metabolite enriched compositions are administered in this assay.

DETD [0309] When **gamma-tocopherol** enriched tocopherol composition (greater than 90% **gamma-tocopherol**) was administered I.V. at the time of MCAO, total infarct volume, total ischemic damage and edema were significantly reduced relative to that of control animals. Administration of the **gamma-tocopherol** metabolite, gamma-CEHC, I.V. at the time of MCAO also resulted in significantly reduced total infarct volume and total ischemic damage. . . the time of MCAO also resulted in reduced tissue edema relative to that of control animals. Thus, administration of a **gamma-tocopherol** enriched composition or a **gamma-tocopherol** metabolite enriched composition provided protection to the brain against damage and effects associated with **cerebral ischemia**.

DETD [0310] Administration of a **gamma-tocopherol** enriched composition or a **gamma-tocopherol** metabolite enriched composition at the time of reperfusion resulted in reduction of total infarct volume, total ischemic damage and tissue. . .

DETD [0311] The protective effects of alpha-tocopherol and delta-tocopherol were also assessed in the MCAO assay. At the same concentration, **gamma-tocopherol** was more effective in the reduction of total infarct volume and in the reduction of tissue edema than alpha-or. . .

DETD Animal Assay for Behavioral Recovery after **Cerebral Ischemia**

DETD [0312] This assay is used to assess the efficacy of the test agents in behavioral recovery after **cerebral ischemia** induced in rats. Clinical behavior evaluation includes neurological examination, sensomotor activity and learning and memory behavior testing.

DETD . . . weight after intervention (drug treatment) indicates improvement. In experiments carried out in support of the present invention, intervention with a **gamma-tocopherol**

enriched composition (>65% **gamma-tocopherol**)
resulted in reduction in heart weight with no decrease in left
ventricular systolic pressure (LVSP). By way of comparison, captopril.
. .

CLM What is claimed is:

3. The method of claim 1 wherein said tissue ischemic condition is selected from the group consisting of **cerebral ischemia**; intestinal ischemia; spinal cord ischemia; cardiovascular ischemia; myocardial ischemia associated with myocardial infarction; myocardial ischemia associated with CHF, ischemia associated. . .

4. The method of claim 1 wherein said tissue ischemic condition is **cerebral ischemia**.

23. The method of claim 21 wherein said tissue ischemic condition is selected from the group consisting of **cerebral ischemia**; intestinal ischemia; spinal cord ischemia; cardiovascular ischemia; myocardial ischemia associated with myocardial infarction; myocardial ischemia associated with CHF, ischemia associated. . .

24. The method of claim 21 wherein said tissue ischemia is **cerebral ischemia**.

41. A method for treating and/or ameliorating the symptoms of a non-cardiovascular tissue ischemic condition in a mammalian subject, comprising administering to the subject an effective amount of a **gamma-tocopherol** enriched tocopherol composition, and by said administering, reducing tissue damage related to said non-cardiovascular tissue ischemic condition.

. . . of a non-cardiovascular tissue ischemic condition in a mammalian subject, comprising administering to the subject an effective amount of a **gamma-tocopherol** metabolite enriched composition, and by said administering, reducing tissue damage related to said non-cardiovascular tissue ischemic condition.

44. The method of claim 41 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 60% **gamma-tocopherol**.

45. The method of claim 41 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 65% **gamma-tocopherol**.

46. The method of claim 41 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 70% **gamma-tocopherol**.

47. The method of claim 41 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 75% **gamma-tocopherol**.

48. The method of claim 41 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 80% **gamma-tocopherol**.

49. The method of claim 41 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 85% **gamma-tocopherol**.

50. The method of claim 41 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 90% **gamma-tocopherol**.

51. The method of claim 41 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 95% **gamma-tocopherol**.

52. The method of claim 41 wherein said **gamma-tocopherol** enriched tocopherol composition comprises at least 98% **gamma-tocopherol**.

53. The method of claim 42 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 80% **gamma-tocopherol** metabolite.

54. The method of claim 42 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 85% **gamma-tocopherol** metabolite.

55. The method of claim 42 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 90% **gamma-tocopherol** metabolite.

56. The method of claim 42 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 95% **gamma-tocopherol** metabolite.

57. The method of claim 42 wherein said **gamma-tocopherol** metabolite enriched composition comprises at least 98% **gamma-tocopherol** metabolite.

62. The method of claim 41 wherein said composition comprises **gamma-tocopherol** in a range of about 1 to about 1000 mg per kg body weight of said mammalian subject.

63. The method of claim 41 wherein said composition comprises **gamma-tocopherol** in a range of about 1 to about 50 mg per kg body weight of said mammalian subject.

64. The method of claim 41 wherein said composition comprises **gamma-tocopherol** in a range of about 10 to about 100 mg per kg body weight of said mammalian subject.

67. The method of claim 65 wherein said tissue ischemic conditions is **cerebral ischemia**.

83. The method of claim 82 wherein said tissue ischemic condition is **cerebral ischemia**.

85. The method of claim 82 wherein said non-alpha tocopherol is selected from the group consisting of **gamma-tocopherol**, beta-tocopherol, delta-tocopherol, a **gamma-tocopherol** metabolite, a beta-tocopherol metabolite, and a delta-tocopherol metabolite.

86. The method of claim 82 wherein said non-alpha tocopherol is **gamma-tocopherol**.

87. The method of claim 82 wherein said non-alpha-tocopherol is a **gamma-tocopherol** metabolite.

88. The method of claim 82 wherein said composition comprises **gamma-tocopherol** and two flavonoids.

89. The method of claim 82 wherein said composition comprises **gamma-tocopherol**, quercetin and hesperetin.

91. The method of claim 82 wherein said composition comprises **gamma-tocopherol** in the range of about 1 to about 1000 mg/kg body weight of mammalian subject, hesperetin in the range of. .

92. The method of claim 82 wherein said composition comprises **gamma-tocopherol** in the range of about 1 to about 50

mg/kg body weight of mammalian subject, hesperetin in the range of. .
.
93. The method of claim 82 wherein said composition comprises **gamma-tocopherol** in the range of about 10 to about 100 mg/kg body weight of mammalian subject, hesperetin in the range of. .
.

L10 ANSWER 5 OF 7 USPATFULL
AN 2001:202682 USPATFULL
TI Therapeutic methods employing disulfide derivatives of dithiocarbonates and compositions useful therefor
IN Lai, Ching-San, Encinitas, CA, United States
Vassilev, Vassil, San Diego, CA, United States
PA Medinox, Inc., San Diego, CA, United States (U.S. corporation)
PI US 6316502 B1 20011113
AI US 2000-565666 20000505 (9)
RLI Division of Ser. No. US 1998-103639, filed on 23 Jun 1998, now patented, Pat. No. US 6093743
DT Utility
FS GRANTED
EXNAM Primary Examiner: Weddington, Kevin E.
LREP Reiter, Stephen E.Foley & Lardner
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN 11 Drawing Figure(s); 5 Drawing Page(s)
LN.CNT 2591
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides a novel dithiocarbamamte disulfide dimer useful in various therapeutic treatments, either alone or in combination with other active agents. In one method, the disulfide derivative of a dithiocarbamate is coadministered with an agent that inactivates (or inhibits the production of) species that induce the expression of nitric oxide synthase to reduce the production of such species, while, at the same time reducing nitric oxide levels in the subject. In another embodiment, free iron ion levels are reduced in a subject by administration of a disulfide derivative of a dithiocarbamate(s) to scavenge free iron ions, for example, in subjects undergoing anthracycline chemotherapy. In another embodiment, cyanide levels are reduced in a subject by administration of a disulfide derivative of a dithiocarbamate so as to bind cyanide in the subject. In a further aspect, the present invention relates to compositions and formulations useful in such therapeutic methods.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . of inflammatory cytokines, toxic shock syndrome, adult respiratory distress syndrome, cachexia, myocarditis, autoimmune disorders, eczema, psoriasis, heart failure, dermatitis, urticaria, **cerebral ischemia**, systemic lupus erythematosis, AIDS, AIDS dementia, neurodegenerative disorders (e.g., chronic neurodegenerative disease), chronic pain, priapism, cystic fibrosis, amyotrophic lateral sclerosis,. . .
DETD . . . range of disease states and/or indications, such as, for example, septic shock, hemorrhagic shock, anaphylactic shock, toxic shock syndrome, ischemia, **cerebral ischemia**, administration of cytokines, overexpression of cytokines, ulcers, inflammatory bowel disease (e.g., gastritis, ulcerative colitis or Crohn's disease), diabetes, arthritis, asthma,. . .
DETD . . . IL-2 fusion toxin, DAB.sub.389 IL-2, and the like), IL-4 antagonists (e.g., IL-4 fusion toxin, DAB.sub.389 IL-4, and the like), immune-mediated **neuronal damage** inhibitors, immunoglobins, immunostimulants (e.g., poly-ICLC, edelfosine, ET-18-OCH3, ET-18-OME, and the like), immunosuppressants (e.g., azathioprine, castanospermine, tacrolimus, FK-506, Fujimycin, Prograf, anti-leukointegrin. . .
DETD . . . myocarditis, multiple sclerosis, diabetes mellitus, autoimmune disorders, eczema, psoriasis, glomerulonephritis, heart failure, heart disease, atherosclerosis, Crohn's disease, dermatitis, urticaria,

ischemia, **cerebral ischemia**, systemic lupus erythematosis, AIDS, AIDS dementia, chronic neurodegenerative disease, chronic pain, priapism, cystic fibrosis, amyotrophic lateral sclerosis, schizophrenia, depression, premenstrual. . .

DETD Antioxidants contemplated for use in the above-described topical formulations include superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, .**gamma**.-**tocopherol**, .alpha.-tocopherol, ubiquinol 10, ubiquinone 10, ascorbic acid, uric acid, glutathione, and the like.

CLM What is claimed is:

. . . myocarditis, multiple sclerosis, diabetes mellitus, autoimmune disorders, eczema, psoriasis, glomerulonephritis, heart failure, heart disease, atherosclerosis, Crohn's disease, dermatitis, urticaria, ischemia, **cerebral ischemia**, systemic lupus erythematosis, AIDS, AIDS dementia, chronic neurodegenerative disease, chronic pain, priapism, cystic fibrosis, amyotrophic lateral sclerosis, schizophrenia, depression, premenstrual. . .

L10 ANSWER 6 OF 7 USPATFULL

AN 2001:131342 USPATFULL

TI Conjugates of dithiocarbamate disulfides with pharmacologically active agents and uses therefor

IN Lai, Ching-San, Encinitas, CA, United States
Vassilev, Vassil P., San Diego, CA, United States
Wang, Tingmin, San Marcos, CA, United States

PA Medinox, Inc., San Diego, CA, United States (U.S. corporation)

PI US 6274627 B1 20010814

AI US 1999-416619 19991012 (9)

DT Utility

FS GRANTED

EXNAM Primary Examiner: Weddington, Kevin E.

LREP Reiter, Stephen E.Foley & Lardner

CLMN Number of Claims: 9

ECL Exemplary Claim: 1

DRWN 4 Drawing Figure(s); 5 Drawing Page(s)

LN.CNT 2173

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB In accordance with the present invention, there are provided conjugates of physiologically compatible free radical scavengers (e.g., dithiocarbamate disulfides (DD)) and pharmacologically active agents (e.g., NSAIDS). Invention conjugates provide a new class of pharmacologically active agents (e.g., anti-inflammatory agents) which cause a much lower incidence of side-effects due to the protective effects imparted by modifying the pharmacologically active agents as described herein. In addition, invention conjugates are more effective than unmodified pharmacologically active agents because cells and tissues contacted by the pharmacologically active agent(s) are protected from the potentially damaging effects of free radical overproduction induced thereby as a result of the co-production of free radical scavenger (e.g., dithiocarbamate), in addition to free pharmacologically active agent, when invention conjugate is cleaved.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . invention include inflammatory and infectious diseases, such as, for example, septic shock, hemorrhagic shock, anaphylactic shock, toxic shock syndrome, ischemia, **cerebral ischemia**, administration of cytokines, overexpression of cytokines, ulcers, inflammatory bowel disease (e.g., gastritis, ulcerative colitis or Crohn's disease), diabetes, arthritis, asthma,. . .

DETD . . . FK-506, FR-900506, Fujimycin, Prograf, IL-2 fusion toxin, and DAB.sub.389 IL-2), IL-4 antagonists (e.g., IL-4 fusion toxin, and DAB.sub.389 IL-4), immune-mediated **neuronal damage** inhibitors (e.g., NBI-114, NBI-115, and NBI-116), immunoglobins, immunostimulants (e.g., poly-ICLC, edelfosine, ALP, ET-18-OCH3, ET-18-OME, NSC-24, and poly-IC+poly-L-lysine+carboxymethyl-cellulose), immunosuppressants (e.g., azathioprine,. . .

DETD Antioxidants contemplated for use in the above-described topical

formulations include superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, .**gamma**.-**tocopherol**, .alpha.-tocopherol, ubiquinol 10, ubiquinone 10, ascorbic acid, uric acid, glutathione, and the like.

CLM What is claimed is:

. . . of inflammatory cytokines, toxic shock syndrome, adult respiratory distress syndrome, cachexia, myocarditis, autoimmune disorders, eczema, psoriasis, heart failure, dermatitis, urticaria, **cerebral ischemia**, systemic lupus erythematosis, AIDS, AIDS dementia, chronic neurodegenerative disease, chronic pain, priapism, cystic fibrosis, amyotrophic lateral sclerosis, schizophrenia, depression, premenstrual. . .

L10 ANSWER 7 OF 7 USPATFULL

AN 2000:95042 USPATFULL

TI Therapeutic methods employing disulfide derivatives of dithiocarbamates and compositions useful therefor

IN Lai, Ching-San, Encinitas, CA, United States
Vassilev, Vassil, San Diego, CA, United States

PA Medinox Inc., San Diego, CA, United States (U.S. corporation)

PI US 6093743 20000725

AI US 1998-103639 19980623 (9)

DT Utility

FS Granted

EXNAM Primary Examiner: Weddington, Kevin E.

LREP Gary Cary Ware & Freidenrich, Reiter, Stephen E., Kirschenbaum, Shelia R.

CLMN Number of Claims: 51

ECL Exemplary Claim: 1

DRWN 11 Drawing Figure(s); 5 Drawing Page(s)

LN.CNT 2691

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a novel dithiocarbamate disulfide dimer useful in various therapeutic treatments, either alone or in combination with other active agents. In one method, the disulfide derivative of a dithiocarbamate is coadministered with an agent that inactivates (or inhibits the production of) species that induce the expression of nitric oxide synthase to reduce the production of such species, while, at the same time reducing nitric oxide levels in the subject. In another embodiment, free iron ion levels are reduced in a subject by administration of a disulfide derivative of a dithiocarbamate(s) to scavenge free iron ions, for example, in subjects undergoing anthracycline chemotherapy. In another embodiment, cyanide levels are reduced in a subject by administration of a disulfide derivative of a dithiocarbamate so as to bind cyanide in the subject. In a further aspect, the present invention relates to compositions and formulations useful in such therapeutic methods.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . of inflammatory cytokines, toxic shock syndrome, adult respiratory distress syndrome, cachexia, myocarditis, autoimmune disorders, eczema, psoriasis, heart failure, dermatitis, urticaria, **cerebral ischemia**, systemic lupus erythematosis, AIDS, AIDS dementia, neurodegenerative disorders (e.g., chronic neurodegenerative disease), chronic pain, priapism, cystic fibrosis, amyotrophic lateral sclerosis,. . .

DETD . . . range of disease states and/or indications, such as, for example, septic shock, hemorrhagic shock, anaphylactic shock, toxic shock syndrome, ischemia, **cerebral ischemia**, administration of cytokines, overexpression of cytokines, ulcers, inflammatory bowel disease (e.g., gastritis, ulcerative colitis or Crohn's disease), diabetes, arthritis, asthma,. . .

DETD . . . IL-2 fusion toxin, DAB.sub.389 IL-2, and the like), IL-4 antagonists (e.g., IL-4 fusion toxin, DAB.sub.389 IL-4, and the like), immune-mediated **neuronal damage** inhibitors, immunoglobins, immunostimulants (e.g., poly-ICLC, edelfosine, ET-18-OCH-3, ET-18-OME, and the like), immunosuppressants (e.g., azathioprine,

castanospermine, tacrolimus, FK-506, Fujimycin, Prograf,. . .
DETD Antioxidants contemplated for use in the above-described topical formulations include superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, .**gamma**.-**tocopherol** , .alpha.-tocopherol, ubiquinol 10, ubiquinone 10, ascorbic acid, uric acid, glutathione, and the like.
CLM What is claimed is:
. . . of inflammatory cytokines, toxic shock syndrome, adult respiratory distress syndrome, cachexia, myocarditis, autoimmune disorders, eczema, psoriasis, heart failure, dermatitis, urticaria, **cerebral ischemia**, systemic lupus erythematosis, AIDS, AIDS dementia, chronic neurodegenerative disease, chronic pain, priapism, cystic fibrosis, amyotrophic lateral sclerosis, schizophrenia, depression, premenstrual. . .

```
=> s l2 and l6 and l7
L11          0 L2 AND L6 AND L7

=> s l1 and l5 and l8
L12          0 L1 AND L5 AND L8

=> s l1 and l4 and l7
L13          3 L1 AND L4 AND L7

=> d l13 1-3 bib abs kwic
```

L13 ANSWER 1 OF 3 IFIPAT COPYRIGHT 2003 IFI
AN 10199343 IFIPAT;IFIUDB;IFICDB
TI COMPOSITIONS AND METHODS FOR THE PREVENTION AND TREATMENT OF **CEREBRAL ISCHEMIA**
INF Boddupalli; Sekhar, San Jose, CA, US
Brown; Lesley A., San Jose, CA, US
Del Balzo; Ughetta, Morgan Hill, CA, US
Flaim; Stephen, San Diego, CA, US
Miller; Guy Michael, San Jose, CA, US
Wang; Bing, Cupertino, CA, US
IN Boddupalli Sekhar; Brown Lesley A; Del Balzo Ughetta; Flaim Stephen; Miller Guy Michael; Wang Bing
PAF Unassigned
PA Unassigned Or Assigned To Individual (68000)
AG Gladys H. Monroy Morrison & Foerster LLP, 755 Page Mill Road, Palo Alto, CA, 94304-1018 US
PI US 2002143049 A1 20021003
AI US 2001-20450 20011214
PRAI US 2000-256269P 20001215 (Provisional)
US 2001-296580P 20010606 (Provisional)
FI US 2002143049 20021003
DT Utility; Patent Application - First Publication
FS CHEMICAL
APPLICATION
CLMN 57
GI 4 Figure(s).
FIG. 1 shows the effect of gamma-tocopherol and its metabolite, gamma-carboxy ethyl hydroxy chroman (gamma-CEHC), on the volumetric comparison of total infarct with administration of gamma-tocopherol and gamma-CEHC at the time of Middle Cerebral Artery Occlusion (MCAO) as described in Example 2.
FIG. 2 shows the effect of gamma-tocopherol and its metabolite, gamma-CEHC, on the volumetric comparison of total infarct with administration of gamma-tocopherol and gamma-CEHC at reperfusion as described in Example 2.
FIG. 3 illustrates 5 general formulas of tocopherol metabolites.
FIG. 4 shows the effect of gamma-tocopherol on stroke protection as measured in **cerebral ischemia** MCAO model.
AB The present invention provides compositions and methods for the treatment of **cerebral ischemia**. In particular, the present

invention provides gamma-, beta-, or delta-tocopherol enriched tocopherol compositions and gamma-, beta-, or delta-tocopherol metabolite enriched compositions and methods for their use in preventing or treating a cerebral ischemic condition. The present invention also provides pharmaceutical compositions comprising gamma-, beta-, or delta-tocopherol enriched tocopherol composition or a gamma-, beta-, or delta-tocopherol metabolite enriched composition in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition.

CLMN 57 4 Figure(s).

FIG. 1 shows the effect of gamma-tocopherol and its metabolite, gamma-carboxy ethyl hydroxy chroman (gamma-CEHC), on the volumetric comparison of total infarct with administration of gamma-tocopherol and gamma-CEHC at the time of Middle Cerebral Artery Occlusion (MCAO) as described in Example 2.

FIG. 2 shows the effect of gamma-tocopherol and its metabolite, gamma-CEHC, on the volumetric comparison of total infarct with administration of gamma-tocopherol and gamma-CEHC at reperfusion as described in Example 2.

FIG. 3 illustrates 5 general formulas of tocopherol metabolites.

FIG. 4 shows the effect of gamma-tocopherol on stroke protection as measured in **cerebral ischemia** MCAO model.

TI COMPOSITIONS AND METHODS FOR THE PREVENTION AND TREATMENT OF **CEREBRAL ISCHEMIA**

AB The present invention provides compositions and methods for the treatment of **cerebral ischemia**. In particular, the present invention provides gamma-, beta-, or delta-tocopherol enriched tocopherol compositions and gamma-, beta-, or delta-tocopherol metabolite enriched. . . . or delta-tocopherol enriched tocopherol composition or a gamma-, beta-, or delta-tocopherol metabolite enriched composition in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition.

GI . . .

3 illustrates 5 general formulas of tocopherol metabolites.

FIG. 4 shows the effect of gamma-tocopherol on stroke protection as measured in **cerebral ischemia** MCAO model.

ECLM . . . comprising administering to the subject an effective amount of a non-alpha tocopherol enriched tocopherol composition, and by said administering, reducing **neuronal damage** related to said cerebral ischemic condition.

ACLM 4. The method of claim 1 wherein the non-alpha tocopherol enriched tocopherol composition is a **beta-tocopherol** enriched tocopherol composition.

5. The method of claim 1 wherein the non-alpha tocopherol enriched tocopherol composition is a **beta-tocopherol** metabolite enriched composition.

11. The method of claim 1 wherein the **cerebral ischemia** is due to a spasm of the coronary vasculature.

33. The method of claim 4 wherein said **beta-tocopherol** enriched tocopherol composition comprises at least 50% **beta-tocopherol**.

34. The method of claim 4 wherein said **beta-tocopherol** enriched tocopherol composition comprises at least 65% **beta-tocopherol**.

35. The method of claim 4 wherein said **beta-tocopherol** enriched tocopherol composition comprises at least 75% **beta-tocopherol**.

36. The method of claim 4 wherein said **beta-tocopherol** enriched tocopherol composition comprises at least 90% **beta-tocopherol**.

37. The method of claim 4 wherein said **beta-tocopherol** enriched tocopherol composition comprises at least 95% **beta-tocopherol**.

38. The method of claim 4 wherein said **beta-tocopherol** enriched tocopherol composition comprises at least 98% **beta-tocopherol**.

39. The method of claim 5 wherein said **beta-tocopherol**

metabolite enriched composition comprises at least 50% **beta-tocopherol** metabolite.
40. The method of claim 5 wherein said **beta-tocopherol** metabolite enriched composition comprises at least 65% **beta-tocopherol** metabolite.
41. The method of claim 5 wherein said **beta-tocopherol** metabolite enriched composition comprises at least 90% **beta-tocopherol** metabolite.

L13 ANSWER 2 OF 3 USPATFULL
AN 2002:259473 USPATFULL
TI Compositions and methods for the prevention and treatment of **cerebral ischemia**
IN Miller, Guy Michael, San Jose, CA, UNITED STATES
Brown, Lesley A., San Jose, CA, UNITED STATES
Del Balzo, Ughetta, Morgan Hill, CA, UNITED STATES
Flaim, Stephen, San Diego, CA, UNITED STATES
Boddupalli, Sekhar, San Jose, CA, UNITED STATES
Wang, Bing, Cupertino, CA, UNITED STATES
PI US 2002143049 A1 20021003
AI US 2001-20450 A1 20011214 (10)
PRAI US 2000-256269P 20001215 (60)
US 2001-296580P 20010606 (60)
DT Utility
FS APPLICATION
LREP Gladys H. Monroy, Morrison & Foerster LLP, 755 Page Mill Road, Palo Alto, CA, 94304-1018
CLMN Number of Claims: 57
ECL Exemplary Claim: 1
DRWN 4 Drawing Page(s)
LN.CNT 2288
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides compositions and methods for the treatment of **cerebral ischemia**. In particular, the present invention provides gamma-, beta-, or delta-tocopherol enriched tocopherol compositions and gamma-, beta-, or delta-tocopherol metabolite enriched compositions and methods for their use in preventing or treating a cerebral ischemic condition. The present invention also provides pharmaceutical compositions comprising gamma-, beta-, or delta-tocopherol enriched tocopherol composition or a gamma-, beta-, or delta-tocopherol metabolite enriched composition in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Compositions and methods for the prevention and treatment of **cerebral ischemia**
AB The present invention provides compositions and methods for the treatment of **cerebral ischemia**. In particular, the present invention provides gamma-, beta-, or delta-tocopherol enriched tocopherol compositions and gamma-, beta-, or delta-tocopherol metabolite enriched. . . or delta-tocopherol enriched tocopherol composition or a gamma-, beta-, or delta-tocopherol metabolite enriched composition in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition.
SUMM [0002] This invention generally relates to compositions and methods comprising gamma-tocopherol and/or a metabolite and/or a derivative thereof; **beta-tocopherol** and/or a metabolite and/or a derivative thereof; and delta-tocopherol and/or a metabolite and/or derivative thereof, for preventing or treating **cerebral ischemia** in a mammalian subject. The invention also relates to methods of making such compositions.
SUMM [0003] Ischemia may be defined as the loss of blood flow to a tissue. **Cerebral ischemia**, also known as stroke, is the interruption or reduction of blood flow in the arteries feeding the brain. Loss of. . .
SUMM . . . 6,150,402; 6,083,982; 6,048,891, and 6,242,479 specifically

incorporated herein in their entirety. Alpha-tocopherol has been alleged to have an effect on **cerebral ischemia**. Yamamoto et al., 1983, Stroke, vol. 14:977-982; Hara et al., 1990, Brain Research, vol. 510:335-338; and Altura, et al., 1996,. . .

SUMM . . . 32:107-110. Alpha-tocopherol has a greater antioxidant activity than the other tocopherols. Fukuzawa et al. (1982) Lipids 17:511-13. Alpha-tocopherol, but not **beta-tocopherol**, inhibits protein kinase C function. Ricciarelli et al. (1998) Biochem. J. 334:243-249. However, both alpha- and **beta-tocopherol** inhibit porcine pancreatic phospholipase A2 activity. Grau et al. (1998) Chem. Phys. Lipids 91:109-118. Alpha-, beta-, gamma- and delta-tocopherol were. . .

SUMM [0006] In the treatment of **cerebral ischemia**, free radical scavengers/antioxidants have been used to improve cerebral blood flow and/or neurological outcome. In general, the effects of these. . . (1991) Proc. Natl. Acad. Sci. USA 88:11158-11162. Other compounds, such as lubeluzole, have been shown to have clinical benefit for **cerebral ischemia** but with a very narrow margin of safety. Diener et al. (1995) Stroke 26:30.

SUMM [0007] **Cerebral ischemia** is one of the major causes of human neurological morbidity and mortality with poor prognosis associated with stroke recovery. Thus,. . . for identification of effective compositions and methods which aid in the survival and recovery of cells during injury associated with **cerebral ischemia** or for mammalian subjects at risk for injury associated with **cerebral ischemia**.

SUMM [0009] The present invention relates to compositions and methods for the treatment and prevention of **cerebral ischemia** in a mammalian subject. Accordingly, the present invention provides methods for treating and/or ameliorating the symptoms of a cerebral ischemic. . . comprising administering to the subject an effective amount of a non-alpha tocopherol enriched tocopherol composition, and by said administering, reducing **neuronal damage** related to said cerebral ischemic condition. In some embodiments, the non-alpha tocopherol enriched tocopherol composition is a gamma-tocopherol enriched tocopherol. . . enriched tocopherol composition is a gamma-tocopherol metabolite enriched composition. In additional embodiments, the non-alpha tocopherol enriched tocopherol composition is a **beta-tocopherol** enriched tocopherol composition. In further embodiments, the non-alpha tocopherol enriched tocopherol composition is a **beta-tocopherol** metabolite enriched composition. In yet other embodiments, the non-alpha tocopherol enriched tocopherol composition is a delta-tocopherol enriched tocopherol composition. In. . .

SUMM . . . occlusion of the cerebral vasculature and in other embodiments, the occlusion is due to a thromboembolis. In further embodiments, the **cerebral ischemia** is due to a spasm of the coronary vasculature. In additional embodiments, the cerebral ischemic condition is secondary to a. . .

SUMM . . . least 80%, at least 85%, at least 90%, at least 95%, or at least 98% gamma-tocopherol. In other aspects, a **beta-tocopherol** enriched tocopherol composition comprises at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% **beta-tocopherol**. In yet other aspects, a delta-tocopherol enriched tocopherol composition comprises at least 50%, at least 55%, at least 60%, at. . . least 95%, or at least 98% gamma-tocopherol metabolite. In some embodiments, the gamma-tocopherol metabolite is gamma-CEHC. In other aspects, a **beta-tocopherol** metabolite enriched composition comprises at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% **beta-tocopherol** metabolite. In yet other aspects, a delta-tocopherol metabolite enriched composition comprises at least 50%, at least 55%, at least 60%,. . .

SUMM . . . In other aspects the present invention provides gamma-tocopherol enriched tocopherol compositions comprising gamma

tocopherol in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition. In further embodiments, the present invention provides **beta-tocopherol** enriched tocopherol compositions comprising **beta tocopherol** in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition. In further embodiments, the present invention provides delta-tocopherol enriched tocopherol compositions comprising delta tocopherol in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition.

SUMM . . . provides gamma-tocopherol metabolite or derivative enriched compositions comprising a gamma tocopherol metabolite or derivative in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition. In preferred embodiments, the gamma-tocopherol metabolite is gamma-CEHC. In further embodiments, the present invention provides **beta-tocopherol** metabolite or derivative enriched compositions comprising a **beta tocopherol** metabolite or derivative in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition. In further embodiments, the present invention provides delta-tocopherol metabolite or derivative enriched compositions comprising a delta tocopherol metabolite or derivative in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition.

DRWD [0019] FIG. 4 shows the effect of gamma-tocopherol on stroke protection as measured in **cerebral ischemia** MCAO model.

DETD . . . and non-naturally occurring mixtures of naturally-occurring compounds that can be used in nutritional and pharmaceutical compositions that are protective in **cerebral ischemia** (stroke). The present invention provides compositions and methods for preventing or treating **cerebral ischemia**, such as for example, by reducing neuronal cell death, reducing tissue edema, and/or reducing cognitive dysfunction associated with a cerebral. . .

DETD [0021] The present invention provides gamma-tocopherol enriched tocopherol compositions, **beta-tocopherol** enriched tocopherol compositions and delta-tocopherol enriched compositions and methods for using such compositions. In preferred embodiments, the gamma-tocopherol enriched tocopherol. . . as the sole active ingredient. As used herein, an "active ingredient" is one that is able to treat or prevent **cerebral ischemia** in a mammalian subject. In preferred embodiments, an active ingredient is able to reduce **neuronal damage** associated with **cerebral ischemia** at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%,. . .

DETD . . . ischemic condition, and/or reduce cognitive dysfunction and may further comprise a gamma-tocopherol metabolite and/or derivative and may further comprise alpha-tocopherol, **beta-tocopherol** and/or delta-tocopherol, and/or other ingredients. In other preferred embodiments, the gamma-tocopherol enriched tocopherol compositions of the present invention comprise additional. . .

DETD [0023] In preferred embodiments, the **beta-tocopherol** enriched tocopherol compositions of the present invention comprise at least 50% **beta-tocopherol**, at least 55% **beta-tocopherol**, at least 60% **beta-tocopherol**, at least 65% **beta-tocopherol**, at least 70% **beta-tocopherol**, at least 75% **beta-tocopherol**, at least 80% **beta-tocopherol**, at least 85% **beta tocopherol**, at least 90% **beta-tocopherol**, at least 95% gamma-tocopherol and at least 98% **beta-tocopherol**. **Beta-tocopherol** enriched tocopherol compositions comprise less than 50% alpha-tocopherol, less than 45% alpha-tocopherol, less than 40% alpha-tocopherol, less than 35% alpha-tocopherol,. . . less than 20% alpha-tocopherol, less than 15% alpha-tocopherol, less than 10% alpha-tocopherol or less than 5% alpha-tocopherol. In some embodiments, **beta-tocopherol** enriched tocopherol compositions comprises **beta-tocopherol** as the sole active

ingredient. In additional preferred embodiments, a **beta-tocopherol** enriched tocopherol composition comprises **beta-tocopherol** in an amount effective to reduce neuronal cell death, reduce infarct size, reduce tissue edema associated with the cerebral ischemic condition, and/or reduce cognitive dysfunction and may further comprise a **beta-tocopherol** metabolite and/or derivative and may further comprise alpha-tocopherol, gamma-tocopherol and/or delta-tocopherol and/or other ingredients. In other preferred embodiments, the **beta-tocopherol** enriched tocopherol compositions of the present invention comprise additional active ingredients, and/or additional non-tocopherols. In some embodiments of **beta-tocopherol** enriched tocopherol compositions, the **beta-tocopherol** and additional ingredient(s) provide a synergistic effect. **Beta-tocopherol** and an additional ingredient are considered to be synergistic when their combined effect is greater than additive of the individual. . .

DETD . . . ischemic condition, and/or reduce cognitive dysfunction and may further comprise a delta-tocopherol metabolite and/or derivative and may further comprise alpha-tocopherol, **beta-tocopherol** and/or gamma-tocopherol and/or other ingredients. In other preferred embodiments, the delta-tocopherol enriched tocopherol compositions of the present invention comprise additional. . .

DETD [0025] Assays for measuring the effect of gamma-tocopherol enriched tocopherol compositions, **beta-tocopherol** enriched compositions and delta-tocopherol compositions are provided herein and are known to those of skill in the art.

DETD [0026] In other aspects the present invention provides gamma-tocopherol metabolite or derivative enriched compositions, **beta-tocopherol** metabolite or derivative enriched compositions, and delta-tocopherol metabolite or derivative enriched compositions, and methods for using such compositions. In preferred embodiments, the gamma-tocopherol metabolite, **beta-tocopherol** metabolite or delta-tocopherol metabolite enriched compositions of the present invention comprise at least 50% gamma-, beta-, or delta-tocopherol metabolite or. . . 90% gamma-, beta-, or delta-tocopherol metabolite or derivative and at least 95% gamma-, beta-, or delta-tocopherol metabolite or derivative. Gamma-tocopherol, **beta-tocopherol** or delta-tocopherol metabolite enriched compositions comprises less than 50% alpha-tocopherol, less than 45% alpha-tocopherol, less than 40% alpha-tocopherol, less than. . . A gamma-, beta-, or delta-tocopherol metabolite or derivative enriched composition may further comprise tocopherol(s). In other preferred embodiments, the gamma-tocopherol, **beta-tocopherol** or delta-tocopherol metabolite or derivative enriched compositions of the present invention comprise additional active ingredients, and/or additional non-tocopherols. In some. . .

DETD . . . of MCAO and at the time of reperfusion, as described in Example 2. In further illustrative embodiments shown herein, a **beta-tocopherol** enriched tocopherol composition is shown to reduce total infarct size at three hours pre-MCAO when administered gavage and a delta-tocopherol. . .

DETD [0029] "**Cerebral Ischemia**" or "cerebral ischemic" or "a cerebral ischemic condition" refer to a medical event which is pathological in origin, or to. . . against and flattens the arteries and veins inside the brain, thereby reducing their ability to carry blood through the brain. **Cerebral ischemia** may also occur as a result of macro- or micro-emboli, such as may occur subsequent to cardiopulmonary bypass surgery.

DETD . . . are characterized by a 6-chromanol ring structure and a side chain at the 2 position. A "gamma-tocopherol enriched tocopherol composition", "**beta-tocopherol** enriched tocopherol composition" or a "delta-tocopherol enriched tocopherol composition" as used herein refers to the particular tocopherol as being enriched. . .

DETD [0032] **beta-tocopherol**, 3,4-dihydro-2,5,8-trimethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-ol; 2,5,8-trimethyl-2-(4,8,12-trimethyltridecyl)-6-chromanol; 5-8-dimethyltocol;

cumotocopherol; neotocopherol; p-xylotocopherol;

DETD [0044] In the body of a subject, gamma-tocopherol, **beta-tocopherol** and delta-tocopherol break down into metabolites, including for example, the metabolites described in Wechter et al. U.S. Pat. Nos. 6,150,402;. . .

DETD . . . that comprises 50% or greater, a tocopherol other than alpha-tocopherol. Examples of non-alpha tocopherol enriched tocopherol compositions include without limitation, **beta-tocopherol** enriched tocopherol compositions, **beta-tocopherol** metabolite enriched compositions, delta-tocopherol enriched tocopherol compositions, delta-tocopherol metabolite enriched compositions, gamma-tocopherol enriched tocopherol compositions, gamma-tocopherol metabolite enriched compositions, epsilon-tocopherol. . .

DETD . . . or "cytoprotective agents" are defined herein as compounds, mixtures, or formulations of compounds which are capable of preventing or treating **cerebral ischemia**, such as by reducing **neuronal damage** or symptoms thereof, associated with a cerebral ischemic condition and/or cell damage due to **cerebral ischemia**. "Amelioration" means the prevention, reduction, palliation, or a counter-acting of the negative aspects of an ischemic condition or ischemic state.. . .

DETD . . . symptoms of a cerebral ischemic condition and/or injury(ies) suffered by cells, tissues, organs and/or organisms that is induced secondary to **cerebral ischemia**. Cytoprotective activity and injury can be quantified in assays which measure results of injury such as death and inhibition of. . .

DETD [0055] By "amounts effective to reduce **neuronal damage** associated with a cerebral ischemic conditions and/or symptoms due to **cerebral ischemia**" is meant that the cytoprotective agent or agents (e.g., gamma-tocopherol, and/or **beta-tocopherol**, and/or delta tocopherol and/or a mixture thereof and/or derivatives and/or metabolites thereof) is present in a final concentration sufficient for reducing injury(ies) associated with a cerebral ischemic condition and/or symptoms due to **cerebral ischemia**. This amount includes, but is not limited to, a concentration which acts as a complete prophylaxis or treatment for a symptom of **neuronal damage**. An "effective amount" is an amount sufficient to effect beneficial or desired results. An effective amount can be administered in. . . least about 70%, even more preferably at least about 80%, and even more preferably at least about 90% reduction in **neuronal damage**.

DETD . . . gamma-tocopherol derivatives and/or other tocopherols, eg, beta- and delta-tocopherol, for use as cytoprotectants against damage, injury(ies) and/or symptoms associated with **cerebral ischemia**. Also provided herein are gamma-tocopherol metabolite enriched compositions comprising gamma-tocopherol metabolite(s) that may further comprise gamma-tocopherol, and/or derivatives thereof, and/or other tocopherol metabolites, for use as cytoprotectants against damage, injury(ies) and/or symptoms associated with **cerebral ischemia**.

DETD [0065] Provided herein are **beta-tocopherol** enriched tocopherol compositions comprising **beta-tocopherol** that may further comprise **beta-tocopherol** metabolites, and/or **beta-tocopherol** derivatives, and/or other tocopherols, eg, gamma- and delta-tocopherolfor use as cytoprotectants against damage, injury(ies) and/or symptoms associated with **cerebral ischemia**. Also provided herein are **beta-tocopherol** metabolite enriched compositions comprising **beta-tocopherol** metabolite(s) that may further comprise **beta-tocopherol**, and/or derivatives thereof, and/or other tocopherol metabolites, for use as cytoprotectants against damage, injury(ies) and/or symptoms associated with **cerebral ischemia**.

DETD . . . enriched tocopherol compositions comprising delta-tocopherol that may further comprise delta-tocopherol metabolites, and/or delta-tocopherol derivatives, and/or other tocopherols, eg gamma- and

beta-tocopherol, for use as cytoprotectants against damage, injury(ies) and/or symptoms associated with **cerebral ischemia**. Also provided herein are delta-tocopherol metabolite enriched compositions comprising delta-tocopherol metabolite(s) that may further comprise delta-tocopherol, and/or derivatives thereof, and/or other tocopherol metabolites, for use as cytoprotectants against damage, injury(ies) and/or symptoms associated with **cerebral ischemia**.

DETD [0067] These compounds are present in the compositions in amounts effective to ameliorate the injury(ies) and/or symptoms associated with **cerebral ischemia**. Preferably gamma-tocopherol enriched compositions comprise at least 50% gamma-tocopherol, at least 55% gamma-tocopherol, at least 60% gamma-tocopherol, at least 65%. . .

DETD [0069] Preferably **beta-tocopherol** enriched compositions comprise at least 50% **beta-tocopherol**, at least 55% **beta-tocopherol**, at least 60% **beta-tocopherol**, at least 65% **beta-tocopherol**, at least 70% **beta-tocopherol**, at least 75% **beta-tocopherol**, at least 80% **beta-tocopherol**, at least 85% **beta tocopherol**, at least 90% **beta-tocopherol** and at least 95% **beta-tocopherol**. **Beta-tocopherol** enriched tocopherol compositions may also comprise **beta-tocopherol** derivative(s) and/or **beta tocopherol** metabolite(s), and/or other tocopherol(s) and/ or mixtures thereof. **Beta-tocopherol** enriched tocopherol compositions comprises less than 50% alpha-tocopherol, less than 45% alpha-tocopherol, less than 40% alpha-tocopherol, less than 35% alpha-tocopherol,. . .

DETD [0070] Preferably, **beta-tocopherol** metabolite enriched compositions comprise at least 50% **beta-tocopherol** metabolite, at least 55% **beta-tocopherol** metabolite, at least 60% **beta-tocopherol** metabolite, at least 65% **beta-tocopherol** metabolite, at least 70% **beta-tocopherol** metabolite, at least 75% **beta-tocopherol** metabolite, at least 80% **beta-tocopherol** metabolite, at least 85% **beta tocopherol** metabolite, at least 90% **beta-tocopherol** metabolite and at least 95% **beta-tocopherol** metabolite. In preferred embodiments, **beta-tocopherol** metabolite enriched compositions comprises less than 50% alpha-tocopherol, less than 45% alpha-tocopherol, less than 40% alpha-tocopherol, less than 35% alpha-tocopherol,. . . than 25% alpha-tocopherol, less than 20% alpha-tocopherol, less than 15% alpha-tocopherol, less than 10% alpha-tocopherol or less than 5% alpha-tocopherol. **Beta-tocopherol** metabolite enriched compositions may also comprise **beta-tocopherol** and/or a **beta tocopherol** derivative(s), and/or other tocopherol(s) and/ or mixtures thereof.

DETD . . . gamma-tocopherol enriched composition was able to reduce infarct size by 77% when administered by gavage at 10.00 mg/kg and a **beta-tocopherol** containing composition (obtained from Matreys, Inc. Pleasant Gap, Pa. and comprising greater than 90% **beta-tocopherol**) when administered gavage at 10.00 mg/kg was able to reduce infarct size by 76%. It was also shown that gamma-CEHC enriched composition decreased **neuronal damage** by 50-65% in drug ranges 0.1-5 mg/kg when administered IV at MCAO.

DETD [0151] gamma-tocopherol enriched composition for gavage administration comprising at least 50% gamma-tocopherol and **beta-tocopherol**;

DETD [0152] **beta-tocopherol** compositions comprising greater than 90% **beta-tocopherol** and more preferably, greater than 95% **beta-tocopherol**; and

DETD . . . include without limitation the use of hippocampal cell assay, animal cerebral infarct assay and animal assay for behavioral recovery

after **cerebral ischemia**. Gamma-, beta-, or delta-tocopherol enriched tocopherol compositions and gamma-, beta-, or delta-tocopherol metabolite enriched compositions suitable for the present invention. . . condition, reduction in infarct size, reduction in cognitive disorder as measured by the methods disclosed in the Examples. Reduction in **neuronal damage** associated with a cerebral ischemic condition is quantified at least about 30%, preferably at least about 50%, more preferably at. . .

DETD [0159] In one aspect, methods of the present invention relate to preventing **neuronal damage** in a mammalian subject at risk of developing injury due to a cerebral ischemic condition, e.g. for example, by an infarct in the brain. The methods of reducing **neuronal damage** relate to minimizing the extent and/or severity of injury in the brain associated with or due to a cerebral ischemic. . . ameliorating or reducing the injury that would otherwise occur. The methods encompass administering a gamma-tocopherol enriched tocopherol composition and/or a **beta-tocopherol** enriched tocopherol composition and/or a delta-tocopherol enriched tocopherol composition and/or a gamma-, beta-, or delta-tocopherol metabolite enriched composition(s) to a. . . subject. The amount administered and the duration of the treatment are effective to minimize the size and/or severity of the **neuronal damage** in the mammalian subject as measured by for example, reduction in neuronal cell death and/or reduction in tissue edema associated. . . in infarct size. Thus, it is anticipated that as a result of such treatment the size and/or severity of any **neuronal damage** that develops is minimized.

DETD [0160] The present invention provides prophylactic treatments for **neuronal damage** including cell death and/or presence of tissue edema and/or cognitive dysfunction and/or cerebral infarcts which may be due to ischemic,. . . gamma-, beta-, or delta-tocopherol metabolite enriched compositions of the present invention are administered to a subject at risk of experiencing **neuronal damage** associated or due to a cerebral ischemic condition, and ameliorates the severity of the damage, should it occur. The method is intended for a subject at risk of **neuronal damage** that is associated with, or results from, an acute or chronic medical condition. Such conditions might arise as a result. . . emergent medical condition such as a stroke or severe blood loss. Other conditions which place a subject at risk for **neuronal damage** associated with a cerebral ischemic condition include a genetic predisposition to stroke or a condition that is understood to increase. . .

DETD [0161] Additional medical conditions that place a subject at risk for **neuronal damage** associated with or due to a cerebral ischemic condition include, but are not limited to, thrombosis; vasculitis (including collagen vascular. . .

DETD [0162] Medical conditions that place a subject at risk of **neuronal damage** associated with or due to a cerebral ischemic condition due to intracranial hemorrhage include, but are not limited to, spontaneous. . .

DETD . . . thereof, in an effective amount. With regard to a cerebral ischemic condition, an effective amount is one sufficient to reduce **neuronal damage** resulting from the cerebral ischemic condition. A reduction of **neuronal damage** is any prevention of injury to the brain which otherwise would have occurred in a subject experiencing a cerebral ischemic. . .

DETD . . . supplements may also be incorporated into food stuffs, such as, functional foods designed to promote cerebral health or to prevent **cerebral ischemia**. If administered as a medicinal preparation, the composition can be administered, either as a prophylaxis or treatment, to a patient. . .

DETD . . . and ex vivo use, a variety of concentrations may be used and various assays employed to determine the degree of **neuronal damage**, such as, for example, measurements of cell death, infarct size, and cognitive dysfunction.

DETD . . . enriched tocopherol compositions, and/or gamma-, beta-, or

delta-tocopherol metabolite enriched compositions, and methods using the compositions are capable of reducing **neuronal damage** associated with **cerebral ischemia**. These conditions can be induced experimentally by chemical interference or by changing the environmental conditions in the laboratory (e.g., by. . .

DETD [0200] Various assays, compositions and methods useful for identifying compositions and methods for reducing **neuronal damage** are provided in the Examples.

DETD [0221] This assay is used to assess the efficacy of the test agents in protecting the brain against necrosis following **cerebral ischemia** induced in rats. Middle Cerebral Artery Occlusion (MCAO) is a widely used technique to induce transient focal **cerebral ischemia** in animal models. It has been demonstrated that the rat model of MCAO is an appropriate approximation of ischemic damage. . .

DETD . . . enriched tocopherol composition or a gamma-tocopherol metabolite enriched composition provided protection to the brain against damage and effects associated with **cerebral ischemia** .

DETD Animal Assay for Behavioral Recovery after **Cerebral Ischemia**

DETD [0266] This assay is used to assess the efficacy of the test agents in behavioral recovery after **cerebral ischemia** induced in rats. Clinical behavior evaluation includes neurological examination, sensomotor activity and learning and memory behavior testing.

CLM What is claimed is:

. . . comprising administering to the subject an effective amount of a non-alpha tocopherol enriched tocopherol composition, and by said administering, reducing **neuronal damage** related to said cerebral ischemic condition.

4. The method of claim 1 wherein the non-alpha tocopherol enriched tocopherol composition is a **beta-tocopherol** enriched tocopherol composition.

5. The method of claim 1 wherein the non-alpha tocopherol enriched tocopherol composition is a **beta-tocopherol** metabolite enriched composition.

11. The method of claim 1 wherein the **cerebral ischemia** is due to a spasm of the coronary vasculature.

33. The method of claim 4 wherein said **beta-tocopherol** enriched tocopherol composition comprises at least 50% **beta-tocopherol**.

34. The method of claim 4 wherein said **beta-tocopherol** enriched tocopherol composition comprises at least 65% **beta-tocopherol**.

35. The method of claim 4 wherein said **beta-tocopherol** enriched tocopherol composition comprises at least 75% **beta-tocopherol**.

36. The method of claim 4 wherein said **beta-tocopherol** enriched tocopherol composition comprises at least 90% **beta-tocopherol**.

37. The method of claim 4 wherein said **beta-tocopherol** enriched tocopherol composition comprises at least 95% **beta-tocopherol**.

38. The method of claim 4 wherein said **beta-tocopherol** enriched tocopherol composition comprises at least 98% **beta-tocopherol**.

39. The method of claim 5 wherein said **beta-tocopherol**

metabolite enriched composition comprises at least 50% **beta-tocopherol** metabolite.

40. The method of claim 5 wherein said **beta-tocopherol** metabolite enriched composition comprises at least 65% **beta-tocopherol** metabolite.

41. The method of claim 5 wherein said **beta-tocopherol** metabolite enriched composition comprises at least 90% **beta-tocopherol** metabolite.

L13 ANSWER 3 OF 3 USPATFULL
AN 2002:243654 USPATFULL
TI Compositions and methods for the prevention and treatment of tissue ischemia
IN Miller, Guy Michael, San Jose, CA, UNITED STATES
Brown, Lesley A., San Jose, CA, UNITED STATES
Del Balzo, Ughetta, Morgan Hill, CA, UNITED STATES
Flaim, Stephen, San Diego, CA, UNITED STATES
Boddupalli, Sekhar, San Jose, CA, UNITED STATES
Wang, Bing, Cupertino, CA, UNITED STATES
PI US 2002132845 A1 20020919
AI US 2001-17717 A1 20011214 (10)
PRAI US 2000-256269P 20001215 (60)
US 2001-296581P 20010606 (60)
US 2001-296580P 20010606 (60)
US 2001-343575P 20011019 (60)
DT Utility
FS APPLICATION
LREP Gladys H. Monroy, Morrison & Foerster LLP, 755 Page Mill Road, Palo Alto, CA, 94304-1018
CLMN Number of Claims: 97
ECL Exemplary Claim: 1
DRWN 7 Drawing Page(s)
LN.CNT 3908
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides compositions and methods for the treatment of tissue ischemia, and in particular, **cerebral ischemia**. In particular, the present invention provides gamma-, beta-, or delta-tocopherol enriched tocopherol compositions and gamma-, beta-, or delta-tocopherol metabolite enriched compositions and/or flavonoid enriched and/or a flavonoid derivative enriched compositions and methods for their use in preventing or treating a tissue ischemic condition or a cerebral ischemic condition. The present invention also provides pharmaceutical compositions comprising gamma-, beta-, or delta-tocopherol enriched tocopherol composition, a gamma-, beta-, or delta-tocopherol metabolite enriched compositions or flavonoid enriched compositions or flavonoid derivative enriched compositions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides compositions and methods for the treatment of tissue ischemia, and in particular, **cerebral ischemia**. In particular, the present invention provides gamma-, beta-, or delta-tocopherol enriched tocopherol compositions and gamma-, beta-, or delta-tocopherol metabolite enriched. . .
SUMM [0002] This invention generally relates to compositions and methods comprising gamma-tocopherol and/or a metabolite and/or a derivative thereof; **beta-tocopherol** and/or a metabolite and/or a derivative thereof; delta-tocopherol and/or a metabolite and/or derivative thereof; and/or a flavonoid and/or a derivative. . .
SUMM [0003] Ischemia may be defined as the loss of blood flow to a tissue. **Cerebral ischemia**, also known as stroke, is the interruption or reduction of blood flow in the arteries feeding the brain. Loss of. . .
SUMM . . . Res. Comm. Mol. Pathol. Pharmacol. 101:259-268; Gebicki et al. (1999) Biochem. J. 338:629-636. ROS are also produced in response to

cerebral ischemia, including that caused by stroke, traumatic head injury and spinal injury. In addition, when metabolism increases or a body is. . .

SUMM . . . 93:6002-6007). See also U.S. Pat. Nos. 6,150,402; 6,083,982; 6,048,891, and 6,242,479. Alpha-tocopherol has been alleged to have an effect on **cerebral ischemia**. Yamamoto et al., 1983, Stroke, vol. 14:977-982; Hara et al., 1990, Brain Research, vol. 510: 335-338; and Altura, et al.,. . .

SUMM . . . in a mammalian subject. The present invention also relates to compositions and methods for treating and/or ameliorating the symptoms of **cerebral ischemia** in a mammalian subject.

Accordingly, the present invention provides methods for treating and/or ameliorating the symptoms of a cerebral ischemic. . . comprising administering to the subject an effective amount of a non-alpha tocopherol enriched tocopherol composition, and by said administering, reducing **neuronal damage** related to said cerebral ischemic condition. In some embodiments, the non-alpha tocopherol enriched tocopherol composition is a gamma-tocopherol enriched tocopherol. . . the non-alpha tocopherol is a gamma-tocopherol metabolite enriched composition. In other embodiments, the non-alpha tocopherol enriched tocopherol composition is a **beta-tocopherol** enriched tocopherol composition. In further embodiments, the non-alpha tocopherol is a **beta-tocopherol** metaoblite enriched composition. In further embodiments, the non-alpha tocopherol enriched tocopherol composition is a delta-tocopherol enriched tocopherol composition. In yet. . . In other aspects the present invention provides gamma-tocopherol enriched tocopherol compositions comprising gamma tocopherol in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition. In further embodiments, the present invention provides **beta-tocopherol** enriched tocopherol compositions comprising **beta tocopherol** in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition. In yet further embodiments, the present invention provides delta-tocopherol enriched tocopherol compositions comprising delta tocopherol in an amount effective to reduce **neuronal damage** related to a cerebral ischemic condition.

SUMM . . . symptoms of a tissue ischemic condition in a mammalian subject, comprising administering to the subject an effective amount of a **beta-tocopherol** enriched tocopherol composition, and by said administering, reducing tissue damage related to said tissue ischemic condition. The present invention also. . . symptoms of a tissue ischemic condition in a mammalian subject, comprising administering to the subject an effective amount of a **beta-tocopherol** metabolite enriched composition, and by said administering, reducing tissue damage related to said tissue ischemic condition. In some embodiments, the tissue ischemic condition is selected from the group consisting of **cerebral ischemia**; intestinal ischemia; spinal cord ischemia; cardiovascular ischemia; myocardial ischemia associated with myocardial infarction; mycardial ischemia associated with CHF, ischemia associated. . . gangrenous conditions, post-trauma syndrome, cardiac arrest resuscitation, peripheral nerve damage or neuropathies. In some embodiments, the tissue ischemic condition is **cerebral ischemia**. In further embodiments, a composition comprises a **beta-tocopherol** in a range of about 1 to about 1000 mg per kg body weight of said mammalian subject. In additional embodiments, a composition comprises a **beta-tocopherol** in a range of about 1 to about 50 mg per kg body weight of said mammalian subject. In yet additional embodiments, a composition comprises a **beta-tocopherol** in a range of about 10 to about 100 mg per kg body weight of said mammalian subject.

SUMM . . . related to said tissue ischemic condition. In some embodiments, the tissue ischemic condition is selected from the group consisting of **cerebral ischemia**; intestinal ischemia; spinal cord ischemia; cardiovascular ischemia; myocardial ischemia associated with

myocardial infarction; mycardial ischemia associated with CHF, ischemia associated. . . gangrenous conditions, post-trauma syndrome, cardiac arrest resuscitation, peripheral nerve damage or neuropathies. In further embodiments, the tissue ischemic condition is **cerebral ischemia**. In further embodiments, a composition comprises a delta-tocopherol in a range of about 1 to about 1000 mg per kg. . .

SUMM . . . by said administering, reducing tissue damage related to said tissue ischemic condition. In some embodiments, the tissue ischemic condition is **cerebral ischemia**. In other embodiments, the tissue ischemic condition is cardiovascular ischemia. In further embodiments, the non-alpha tocopherol is selected from the group consisting of gamma-tocopherol, **beta-tocopherol**, delta-tocopherol, a gamma-tocopherol metabolite, a **beta-tocopherol** metabolite, and a delta-tocopherol metabolite. In further embodiments, the non-alpha tocopherol is gamma-tocopherol. In yet additional embodiments, the non-alpha-tocopherol is. . .

SUMM . . . 70%, at least 80%, at least 90%, at least 95% gamma-tocopherol, or at least 98% gamma-tocopherol. In other aspects, a **beta-tocopherol** enriched tocopherol composition comprises at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% **beta-tocopherol**, or at least 98% **beta-tocopherol**. In yet other aspects, a delta-tocopherol enriched tocopherol composition comprises at least 50%, at least 60%, at least 70%, at. . . least 95%, or at least 98% gamma-tocopherol metabolite. In some embodiments, the gamma-tocopherol metabolite is gamma-CEHC. In other aspects, a **beta-tocopherol** metabolite enriched composition comprises at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 98% **beta-tocopherol** metabolite. In yet other aspects, a delta-tocopherol metabolite enriched composition comprises at least 50%, at least 60%, at least 70%,. . .

SUMM [0022] The present invention also provides compositions comprising a non-alpha tocopherol and a flavonoid in amounts effective to reduce **neuronal damage** related to a cerebral ischemic condition. In some embodiments, the composition comprises hesperetin or quercetin. In other embodiments, the composition. . .

DRWD [0028] FIG. 5 shows the effect of gamma-tocopherol on stroke protection as measured in a **cerebral ischemia** MCAO model.

DETD . . . of naturally-occurring compounds that can be used in nutritional and pharmaceutical compositions that are protective in tissue ischemia, such as **cerebral ischemia** (stroke) and mycardial injury subsequent to ischemia or hypoxia. The present invention provides compositions and methods for treating and/or ameliorating the symptoms of tissue ischemia, such as for example, **cerebral ischemia**, cardiovascular ischemia, spinal cord ischemia, intestinal ischemia, liver ischemia, kidney ischemia, dermal ischemia, and other tissue ischemias by for example. . . size associated with myocardial ischemia. The present invention also provides compositions and methods for treating and/or ameliorating the symptoms of **cerebral ischemia**, such as for example, by reducing neuronal cell death, reducing tissue edema, and/or reducing cognitive dysfunction associated with a cerebral. . .

DETD [0032] The present invention provides gamma-tocopherol enriched tocopherol compositions, **beta-tocopherol** enriched tocopherol compositions and delta-tocopherol enriched compositions and methods for using such compositions. In preferred embodiments, gamma-tocopherol enriched tocopherol compositions. . . an amount effective to reduce cell death, reduce infarct size, reduce tissue edema associated with the ischemic condition, and/or in **cerebral ischemia**, reduce cognitive dysfunction and may further comprise a gamma-tocopherol metabolite and/or derivative and may further comprise additional tocopherols and/or other. . .

DETD [0034] In preferred embodiments, **beta-tocopherol** enriched tocopherol compositions of the present invention comprise at least 50% **beta-tocopherol**, at least 55% **beta-tocopherol**, at least 60% **beta-tocopherol**, at least 65% **beta-tocopherol**, at least 70%

beta-tocopherol, at least 75% **beta-tocopherol**, at least 80% **beta-tocopherol**, at least 85% **beta tocopherol**, at least 90% **beta-tocopherol** and at least 95% **beta-tocopherol**. **Beta-tocopherol** enriched tocopherol compositions comprise less than 50% alpha-tocopherol, less than 45% alpha-tocopherol, less than 40% alpha-tocopherol, less than 35% alpha-tocopherol,. . . less than 20% alpha-tocopherol, less than 15% alpha-tocopherol, less than 10% alpha-tocopherol or less than 5% alpha-tocopherol. In some embodiments, **beta-tocopherol** enriched tocopherol compositions comprise **beta-tocopherol** as the sole active ingredient. In additional preferred embodiments, a **beta-tocopherol** enriched tocopherol composition comprises **beta-tocopherol** in an amount effective to reduce cell death, reduce infarct size, reduce tissue edema associated with the ischemic condition, and/or reduce cognitive dysfunction, such as in **cerebral ischemia** and may further comprise a **beta-tocopherol** metabolite and/or derivative and may further comprise additional tocopherols and/or other ingredients. In other preferred embodiments, the **beta-tocopherol** enriched tocopherol compositions of the present invention comprise additional active ingredients, and/or additional non-tocopherols. In some embodiments of **beta-tocopherol** enriched tocopherol compositions, the **beta-tocopherol** and additional ingredient(s) provide a synergistic effect. **Beta-tocopherol** and an additional ingredient are considered to be synergistic when their combined effect is greater than additive of the individual. . .

DETD . . . cell death, reduce infarct size, reduce tissue edema associated with the ischemic condition, and/or reduce cognitive dysfunction, such as for **cerebral ischemia** and may further comprise a delta-tocopherol metabolite and/or derivative and may further comprise additional tocopherols and/or other ingredients. In other. . .

DETD [0036] Assays for measuring the effect of gamma-tocopherol enriched tocopherol compositions, **beta-tocopherol** enriched compositions and delta-tocopherol compositions are provided herein and are known to those of skill in the art.

DETD [0037] In other aspects, the present invention provides gamma-tocopherol metabolite or derivative enriched compositions, **beta-tocopherol** metabolite or derivative enriched compositions, delta-tocopherol metabolite or derivative enriched compositions, and flavonoid enriched compositions, and methods for using such compositions. In preferred embodiments, the gamma-tocopherol, **beta-tocopherol** or delta-tocopherol metabolite enriched compositions of the present invention comprise at least 50% gamma-, beta-, or delta-tocopherol metabolite or derivative,. . . 90% gamma-, beta-, or delta-tocopherol metabolite or derivative and at least 95% gamma-, beta-, or delta-tocopherol metabolite or derivative. Gamma-tocopherol, **beta-tocopherol** or delta-tocopherol metabolite enriched compositions comprises less than 50% alpha-tocopherol, less than 45% alpha-tocopherol, less than 40% alpha-tocopherol, less than. . . cell death, reduce infarct size, reduce tissue edema associated with the ischemic condition, and/or reduce cognitive dysfunction, such as in **cerebral ischemia**. A gamma-, beta-, or delta-tocopherol metabolite or derivative enriched composition may further comprise tocopherol(s). In other preferred embodiments, the gamma-tocopherol, **beta-tocopherol** or delta-tocopherol metabolite or derivative enriched compositions of the present invention comprise additional active ingredients, and/or additional non-tocopherols. In some. . .

DETD . . . of MCAO and at the time of reperfusion, as described in Example 2. In further illustrative embodiments shown herein, a **beta-tocopherol** enriched tocopherol composition is shown to reduce total infarct size at three hours pre-MCAO when administered gavage and a delta-tocopherol. . .

DETD . . . a region of the tissue is impeded or blocked, either temporarily, as in vasospasm or transient ischemic attach (TIA) in

cerebral ischemia or permanently, as in thrombolic occlusion in **cerebral ischemia**. The affected region is deprived of oxygen and nutrients as a consequence of the ischemic event. This deprivation leads to the injuries of infarction or in the region affected. The present invention encompasses **cerebral ischemia**; intestinal ischemia; spinal cord ischemia; cardiovascular ischemia; ischemia associated with CHF, liver ischemia; kidney ischemia; dermal ischemia; vasoconstriction-induced tissue ischemia,. . . against and flattens the arteries and veins inside the tissue, thereby reducing their ability to carry blood through the tissue. **Cerebral ischemia** may also occur as a result of macro-or micro-emboli, such as may occur subsequent to cardiopulmonary bypass surgery. Age-related macular. . .

DETD [0041] "**Cerebral Ischemia**" or "cerebral ischemic" or "a cerebral ischemic condition" refer to a medical event which is pathological in origin, or to. . . against and flattens the arteries and veins inside the brain, thereby reducing their ability to carry blood through the brain. **Cerebral ischemia** may also occur as a result of macro-or micro-emboli, such as may occur subsequent to cardiopulmonary bypass surgery.

DETD . . . are characterized by a 6-chromanol ring structure and a side chain at the 2 position. A "gamma-tocopherol enriched tocopherol composition", "**beta-tocopherol** enriched tocopherol composition" or a "delta-tocopherol enriched tocopherol composition" as used herein refers to the particular tocopherol as being enriched. . .

DETD [0044] **beta-tocopherol**, 3,4-dihydro-2,5,8-trimethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-ol; 2,5,8-trimethyl-2-(4,8,12-trimethyltridecyl)-6-chromanol; 5-8-dimethyltocol; cumotocopherol; neotocopherol; p-xylotocopherol;

DETD [0056] In the body of a subject, gamma-tocopherol, **beta-tocopherol** and delta-tocopherol break down into metabolites, including for example, the metabolites described in Wechter et al. U.S. Pat. Nos. 6,150,402;. . .

DETD . . . that comprises 50% or greater, a tocopherol other than alpha-tocopherol. Examples of non-alpha tocopherol enriched tocopherol compositions include without limitation, **beta-tocopherol** enriched tocopherol compositions, **beta-tocopherol** metabolite enriched compositions, delta-tocopherol enriched tocopherol compositions, delta-tocopherol metabolite enriched compositions, gamma-tocopherol enriched tocopherol compositions, gamma-tocopherol metabolite enriched compositions, epsilon-tocopherol. . . composition that is enriched in a tocopherol other than gamma-tocopherol. Examples of non-gamma tocopherol enriched tocopherol compositions include without limitation, **beta-tocopherol** enriched tocopherol compositions, **beta-tocopherol** metabolite enriched compositions, delta-tocopherol enriched tocopherol compositions, delta-tocopherol metabolite enriched compositions, gamma-tocopherol enriched tocopherol compositions, gamma-tocopherol metabolite enriched compositions, epsilon-tocopherol. . . is enriched in a tocopherol other than alpha-tocopherol and gamma-tocopherol. Examples of non-alpha, non-gamma-tocopherol enriched tocopherol compositions include without limitation, **beta-tocopherol** enriched tocopherol compositions, **beta-tocopherol** metabolite enriched compositions, delta-tocopherol enriched tocopherol compositions, delta-tocopherol metabolite enriched compositions, gamma-tocopherol enriched tocopherol compositions, gamma-tocopherol metabolite enriched compositions, epsilon-tocopherol. . .

DETD . . . compounds, mixtures, or formulations of compounds which are capable of preventing or treating a tissue ischemia, such as for example, **cerebral ischemia**, such as by reducing tissue or cell damage or symptoms thereof, associated with an ischemic condition and/or cell damage due. . .

DETD . . . tissue ischemic conditions and/or symptoms due to tissue ischemia" is meant that the cytoprotective agent or agents (e.g., gamma-tocopherol, and/or **beta-tocopherol**, and/or delta tocopherol and/or a mixture thereof and/or derivatives and/or

metabolites thereof and/or a flavonoid and/or derivatives thereof) is present. . . a concentration which acts as a complete prophylaxis or treatment for a symptom of cellular or tissue damage, such as **neuronal damage** for **cerebral ischemia**. An "effective amount" is an amount sufficient to effect beneficial or desired results. An effective amount can be administered in. . . a tissue ischemic condition, the size and/or severity of an infarct in the tissue, such as in the brain for **cerebral ischemia**, of the subject may be determined, for example, by various noninvasive radiological procedures and/or by various symptomatic and diagnostic procedures. . . more preferably at least about 80%, and even more preferably at least about 90% reduction in tissue damage, such as **neuronal damage** for **cerebral ischemia**.

DETD . . . gamma-tocopherol metabolites, and/or derivatives thereof, and/or other tocopherol metabolites, for use as cytoprotectants against damage, injury(ies) and/or symptoms associated with **cerebral ischemia**.

DETD . . . comprise gamma-tocopherol, and/or derivatives thereof, and/or other tocopherol metabolites, for use as cytoprotectants against damage, injury(ies) and/or symptoms associated with **cerebral ischemia**.

DETD [0089] Provided herein are **beta-tocopherol** enriched tocopherol compositions comprising **beta-tocopherol** that may further comprise **beta-tocopherol** metabolites, and/or **beta-tocopherol** derivatives, and/or other tocopherols, eg, gamma- and delta-tocopherol for use as cytoprotectants against damage, injury(ies) and/or symptoms associated with tissue ischemia. Also provided herein are **beta-tocopherol** metabolite enriched compositions comprising **beta-tocopherol** metabolite(s) that may further comprise **beta-tocopherol**, and/or derivatives thereof, and/or other tocopherol metabolites, for use as cytoprotectants against damage, injury(ies) and/or symptoms associated with tissue ischemia.

DETD . . . enriched tocopherol compositions comprising delta-tocopherol that may further comprise delta-tocopherol metabolites, and/or delta-tocopherol derivatives, and/or other tocopherols, eg gamma- and **beta-tocopherol**, for use as cytoprotectants against damage, injury(ies) and/or symptoms associated with tissue ischemia. Also provided herein are delta-tocopherol metabolite enriched. . .

DETD . . . enriched compositions and compositions comprising gamma-tocopherol and a flavonoid for use as cytoprotectants against damage, injury(ies) and/or symptoms associated with **cerebral ischemia**.

DETD . . . present in the compositions in amounts effective to ameliorate the injury(ies) and/or symptoms associated with a tissue ischemia, such as **cerebral ischemia**. Preferably gamma-tocopherol enriched compositions comprise at least 50% gamma-tocopherol, at least 55% gamma-tocopherol, at least 60% gamma-tocopherol, at least 65%. . .

DETD [0094] Preferably **beta-tocopherol** enriched compositions comprise at least 50% **beta-tocopherol**, at least 55% **beta-tocopherol**, at least 60% **beta-tocopherol**, at least 65% **beta-tocopherol**, at least 70% **beta-tocopherol**, at least 75% **beta-tocopherol**, at least 80% **beta -tocopherol**, at least 85% **beta tocopherol**, at least 90% **beta-tocopherol** and at least 95% **beta-tocopherol**. **Beta-tocopherol** enriched tocopherol compositions may also comprise **beta-tocopherol** derivative(s) and/or **beta tocopherol** metabolite(s), and/or other tocopherol(s) and/or mixtures thereof. **Beta-tocopherol** enriched tocopherol compositions comprises less than 50% alpha-tocopherol, less than 45% alpha-tocopherol, less than 40% alpha-tocopherol, less than 35% alpha-tocopherol,. . .

DETD [0095] Preferably, **beta-tocopherol** metabolite

enriched compositions comprise at least 50% **beta-tocopherol** metabolite, at least 55% **beta-tocopherol** metabolite, at least 60% **beta-tocopherol** metabolite, at least 65% **beta-tocopherol** metabolite, at least 70% **beta-tocopherol** metabolite, at least 75% **beta-tocopherol** metabolite, at least 80% **beta-tocopherol** metabolite, at least 85% **beta tocopherol** metabolite, at least 90% **beta-tocopherol** metabolite and at least 95% **beta-tocopherol** metabolite. In preferred embodiments, **beta-tocopherol** metabolite enriched compositions comprises less than 50% alpha-tocopherol, less than 45% alpha-tocopherol, less than 40% alpha-tocopherol, less than 35% alpha-tocopherol,. . . than 25% alpha-tocopherol, less than 20% alpha-tocopherol, less than 15% alpha-tocopherol, less than 10% alpha-tocopherol or less than 5% alpha-tocopherol. **Beta-tocopherol** metabolite enriched compositions may also comprise **beta-tocopherol** and/or a **beta tocopherol** derivative(s), and/or other tocopherol(s) and/or mixtures thereof.

DETD . . . metabolite enriched composition, gamma-CEHC (greater than 98% gamma-CEHC) are able to reduce total infarct size in an animal model of **cerebral ischemia**, the middle cerebral artery occlusion (MCAO model), when administered at the time of MCAO and when administered at reperfusion (see. . . at 0.60 mg/kg was able to reduce infarct size by 52%. It was also shown that gamma-CEHC enriched composition decreased **neuronal damage** by 50-65% in drug ranges 0.1-5 mg/kg when administered IV at MCAO.

DETD . . . size by 53% and 77%, respectively, when administered by oral gavage at 4 mg/kg and 10 mg/kg, respectively Similarly, a **beta-tocopherol** containing composition (obtained from Matreys, Inc. Pleasant Gap, Pa. and comprising greater than 90% **beta-tocopherol**) when administered oral gavage pre-MCAO at 10 mg/kg was reduced infarct size by 76%. A delta-tocopherol enriched composition administered by. . .

DETD [0180] gamma-tocopherol enriched composition for gavage administration comprising at least 50% gamma-tocopherol and **beta-tocopherol**;

DETD [0181] **beta-tocopherol** compositions comprising greater than 90% **beta-tocopherol** and more preferably, greater than 95% **beta-tocopherol**; and

DETD . . . include without limitation the use of hippocampal cell assay, animal cerebral infarct assay and animal assay for behavioral recovery after **cerebral ischemia**, and congestive heart failure model (CHF). Gamma-, beta-, or delta-tocopherol enriched tocopherol compositions and gamma-, beta-, or delta-tocopherol metabolite enriched. . . reduction in tissue edema associated with an ischemic condition, reduction in infarct size, reduction in cognitive disorder, such as in **cerebral ischemia**, as measured by the methods disclosed in the Examples. Reduction in cellular or tissue damage associated with a ischemic condition. . .

DETD [0191] compositions comprising **beta-tocopherol** and hesperetin;

DETD [0192] compositions comprising **beta-tocopherol** and quercetin; and

DETD [0193] compositions comprising **beta-tocopherol**, hesperetin and quercetin;

DETD [0198] In one aspect, methods of the present invention relate to preventing **neuronal damage** in a mammalian subject at risk of developing injury due to a cerebral ischemic condition, e.g. for example, by an infarct in the brain. The methods of reducing **neuronal damage** relate to minimizing the extent and/or severity of injury in the brain associated with or due to a cerebral ischemic. . . that would otherwise occur. The methods encompass administering a non-alpha tocopherol, such as, a gamma-tocopherol enriched tocopherol composition and/or a **beta-tocopherol** enriched tocopherol composition and/or a

delta-tocopherol enriched tocopherol composition and/or a gamma-, beta-, or delta-tocopherol metabolite enriched composition, and/or a. . . subject. The amount administered and the duration of the treatment are effective to minimize the size and/or severity of the **neuronal damage** in the mammalian subject as measured by for example, reduction in neuronal cell death and/or reduction in cerebral edema associated. . . in infarct size. Thus, it is anticipated that as a result of such treatment the size and/or severity of any **neuronal damage** that develops is minimized.

DETD [0199] The present invention provides prophylactic treatments for **neuronal damage** including cell death and/or presence of tissue edema and/or cognitive dysfunction and/or cerebral infarcts which may be due to ischemic,. . . flavonoid enriched and/or flavonoid derivative enriched compositions of the present invention are administered to a subject at risk of experiencing **neuronal damage** associated or due to a cerebral ischemic condition, and ameliorates the severity of the damage, should it occur. The method is intended for a subject at risk of **neuronal damage** that is associated with, or results from, an acute or chronic medical condition. Such conditions might arise as a result. . . emergent medical condition such as a stroke or severe blood loss. Other conditions which place a subject at risk for **neuronal damage** associated with a cerebral ischemic condition include a genetic predisposition to stroke or a condition that is understood to increase. . .

DETD [0200] Additional medical conditions that place a subject at risk for **neuronal damage** associated with or due to a cerebral ischemic condition include, but are not limited to, thrombosis; vasculitis (including collagen vascular. . .

DETD [0201] Medical conditions that place a subject at risk of **neuronal damage** associated with or due to a cerebral ischemic condition due to intracranial hemorrhage include, but are not limited to, spontaneous. . .

DETD . . . to a myocardial ischemic condition by ameliorating or reducing the injury that would otherwise occur. The methods encompass administering a **beta-tocopherol** enriched tocopherol composition and/or a delta-tocopherol enriched tocopherol composition and/or a beta-, or delta-tocopherol metabolite enriched composition and/or a flavonoid. . .

DETD . . . ameliorating or reducing the injury that would otherwise occur. The methods encompass administering a gamma-tocopherol enriched tocopherol composition and/or a **beta-tocopherol** enriched tocopherol composition and/or a delta-tocopherol enriched tocopherol composition and/or a gamma-, beta-, or delta-tocopherol metabolite or derivative enriched composition. . .

DETD . . . ameliorating or reducing the injury that would otherwise occur. The methods encompass administering a gamma-tocopherol enriched tocopherol composition and/or a **beta-tocopherol** enriched tocopherol composition and/or a delta-tocopherol enriched tocopherol composition and/or a gamma-, beta-, or delta-tocopherol metabolite or derivative enriched composition. . .

DETD . . . composition in an effective amount. With regard to a cerebral ischemic condition, an effective amount is one sufficient to reduce **neuronal damage** resulting from the cerebral ischemic condition. A reduction of **neuronal damage** is any prevention of injury to the brain which otherwise would have occurred in a subject experiencing a cerebral ischemic. . .

DETD . . . supplements may also be incorporated into food stuffs, such as, functional foods designed to promote cerebral health or to prevent **cerebral ischemia**. If administered as a medicinal preparation, the composition can be administered, either as a prophylaxis or treatment, to a patient. . .

DETD . . . and ex vivo use, a variety of concentrations may be used and various assays employed to determine the degree of **neuronal damage**, such as, for example, measurements of cell death, infarct size, and cognitive dysfunction.

DETD . . . enriched tocopherol compositions, and/or gamma-, beta-, or

delta-tocopherol metabolite enriched compositions, and methods using the compositions are capable of reducing **neuronal damage** associated with **cerebral ischemia**. These conditions can be induced experimentally by chemical interference or by changing the environmental conditions in the laboratory (e.g., by. . .

DETD [0246] Various assays, compositions and methods useful for identifying compositions and methods for reducing **neuronal damage** are provided in the Examples.

DETD [0267] This assay is used to assess the efficacy of the test agents in protecting the brain against necrosis following **cerebral ischemia** induced in rats. Middle Cerebral Artery Occlusion (MCAO) is a widely used technique to induce transient focal **cerebral ischemia** in animal models. It has been demonstrated that the rat model of MCAO is an appropriate approximation of ischemic damage. . .

DETD . . . gamma-tocopherol enriched composition or a gamma-tocopherol metabolite enriched composition provided protection to the brain against damage and effects associated with **cerebral ischemia**

.

DETD Animal Assay for Behavioral Recovery after **Cerebral Ischemia**

DETD [0312] This assay is used to assess the efficacy of the test agents in behavioral recovery after **cerebral ischemia** induced in rats. Clinical behavior evaluation includes neurological examination, sensomotor activity and learning and memory behavior testing.

CLM What is claimed is:

. . . symptoms of a tissue ischemic condition in a mammalian subject, comprising administering to the subject an effective amount of a **beta-tocopherol** enriched tocopherol composition, and by said administering, reducing tissue damage related to said tissue ischemic condition.

. . . symptoms of a tissue ischemic condition in a mammalian subject, comprising administering to the subject an effective amount of a **beta-tocopherol** metabolite enriched composition, and by said administering, reducing tissue damage related to said tissue ischemic condition.

3. The method of claim 1 wherein said tissue ischemic condition is selected from the group consisting of **cerebral ischemia**; intestinal ischemia; spinal cord ischemia; cardiovascular ischemia; myocardial ischemia associated with myocardial infarction; myocardial ischemia associated with CHF, ischemia associated. . .

4. The method of claim 1 wherein said tissue ischemic condition is **cerebral ischemia**.

8. The method of claim 1 wherein said **beta-tocopherol** enriched tocopherol composition comprises at least 50% **beta-tocopherol**.

9. The method of claim 1 wherein said **beta-tocopherol** enriched tocopherol composition comprises at least 75% **beta-tocopherol**.

10. The method of claim 1 wherein said **beta-tocopherol** enriched tocopherol composition comprises at least 90% **beta-tocopherol**.

11. The method of claim 2 wherein said **beta-tocopherol** metabolite enriched composition comprises at least 50% **beta-tocopherol** metabolite.

12. The method of claim 2 wherein said **beta-tocopherol** metabolite enriched composition comprises at least 75% **beta-tocopherol** metabolite.

13. The method of claim 2 wherein said **beta-tocopherol** metabolite enriched composition comprises at least 90% **beta-tocopherol** metabolite.

18. The method of claim 1 wherein said composition comprises a **beta-tocopherol** in a range of about 1 to about 1000 mg per kg body weight of said mammalian subject.

19. The method of claim 1 wherein said composition comprises a **beta-tocopherol** in a range of about 1 to about 50 mg per kg body weight of said mammalian subject.

20. The method of claim 1 wherein said composition comprises a **beta-tocopherol** in a range of about 10 to about 100 mg per kg body weight of said mammalian subject.

23. The method of claim 21 wherein said tissue ischemic condition is selected from the group consisting of **cerebral ischemia**; intestinal ischemia; spinal cord ischemia; cardiovascular ischemia; myocardial ischemia associated with myocardial infarction; myocardial ischemia associated with CHF, ischemia associated. . .

24. The method of claim 21 wherein said tissue ischemia is **cerebral ischemia**.

67. The method of claim 65 wherein said tissue ischemic conditions is **cerebral ischemia**.

83. The method of claim 82 wherein said tissue ischemic condition is **cerebral ischemia**.

85. The method of claim 82 wherein said non-alpha tocopherol is selected from the group consisting of gamma-tocopherol, **beta-tocopherol**, delta-tocopherol, a gamma-tocopherol metabolite, a **beta-tocopherol** metabolite, and a delta-tocopherol metabolite.

```
=> s l1 and l4 and l8
L14          0 L1 AND L4 AND L8

=> s l2 and l6 and l8
L15          0 L2 AND L6 AND L8

=>
```